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A COMPARISON OF HIRUDIN WITH HEPARIN IN THE PREVENTION OF RESTENOSIS AFTER CORONARY ANGIOPLASTY

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Abstract *Background.* The likelihood of restenosis is a major limitation of coronary angioplasty. We studied whether hirudin, a highly selective inhibitor of thrombin with irreversible effects, would prevent restenosis after angioplasty. We compared two regimens of recombinant hirudin with heparin.

Methods. We randomly assigned 1141 patients with unstable angina who were scheduled for angioplasty to receive one of three treatments: (1) a bolus dose of 10,000 IU of heparin followed by an intravenous infusion of heparin for 24 hours and subcutaneous placebo twice daily for three days (382 patients), (2) a bolus dose of 40 mg of hirudin followed by an intravenous infusion of hirudin for 24 hours and subcutaneous placebo twice daily for three days (381 patients), or (3) the same hirudin regimen except that 40 mg of hirudin was given subcutaneously instead of placebo twice daily for three days (378 patients). The primary end point was event-free survival at seven months. Other end points were early cardiac events (within 96 hours), bleeding and other complications of the study treatment, and angiographic measurements of coronary diameter at six months of follow-up.

Results. At seven months, event-free survival was 67.3 percent in the group receiving heparin, 63.5 percent in the group receiving intravenous hirudin, and 68.0 percent in the group receiving both intravenous and subcutaneous hirudin ($P=0.61$). However, the administration of hirudin was associated with a significant reduction in early cardiac events, which occurred in 11.0, 7.9, and 5.6 percent of patients in the respective groups (combined relative risk with hirudin, 0.61; 95 percent confidence interval, 0.41 to 0.90; $P=0.023$). The mean minimal luminal diameters in the respective groups on follow-up angiography at six months were 1.54, 1.47, and 1.56 mm ($P=0.08$).

Conclusions. Although significantly fewer early cardiac events occurred with hirudin than with heparin, hirudin had no apparent benefit with longer-term follow-up. (N Engl J Med 1995;333:757-63.)

PLATELET aggregation, the generation of thrombin, and the release of growth factors at the site of angioplasty have all been implicated in the process of restenosis.[1,2] Consequently, anticoagulants, antiplatelet agents, and specific antithrombin agents have been considered for the prevention of restenosis.[3] Thrombin is the most potent platelet activator known, stimulating the production of platelet-derived growth factor and the secretion of prostacyclin, platelet-activating factor, and plasminogen-activator inhibitor. Thrombin has apparent mitogenic effects on lymphocytes and vascular smooth-muscle cells.[4,5]

Hirudin, a 65-amino-acid compound originally extracted from the salivary gland of the leech, is a specific inhibitor of thrombin. The advantage of hirudin over other serine protease inhibitors is its potency in irreversibly blocking thrombin at multiple sites without the need for circulating antithrombin III.[6] Because of the small size of the hirudin molecule, this substance can inhibit clot-bound thrombin and restrict the further formation of thrombus.[7]

Hirudin has reduced the deposition of platelets after vascular injury in pigs[8] and lowered the rate of restenosis in hypercholesterolemic rabbits,[9] providing a rationale for its use in patients undergoing angioplasty. In this trial we evaluated whether the inhibition of thrombin with hirudin as compared with heparin improved event-free survival in patients undergoing coronary angioplasty.

METHODS

Study Population

Patients with unstable angina and one or more clinically important new or restenotic coronary narrowings suitable for treatment with percutaneous transluminal coronary angioplasty were eligible for the study. From September 1992 through May 1995, 1154 patients from various institutions (listed in the Appendix) were randomized. All had unstable angina, as defined by the new onset of angina pectoris or the worsening of angina (i.e., their condition changed by two or more classes according to the classification system of the Canadian Cardiovascular Society[10] or they needed additional antianginal medication), angina at rest, or both in the preceding three months.[11] The criteria for exclusion from the study were stable angina, a planned multistage angioplasty procedure or stent implantation, myocardial infarction occurring within the preceding two weeks, hypertension, diabetic retinopathy, and body weight over 100 kg.

The study was conducted in accordance with the principles of the Declaration of Helsinki and its subsequent amendments and with the laws and regulations of the countries where the trial took place. Before randomization, each patient gave written informed consent.

Antithrombin Regimens

The patients were randomly assigned in a double-blind fashion to receive recombinant hirudin (Revasc, Ciba-Geigy, Basel, Switzerland[12]) in one of two dose regimens or to receive unfractionated sodium heparin. The randomization was stratified according to whether heparin had been administered in the preceding 24 hours. Heparin therapy had to be discontinued at least 30 minutes before the start of treatment with the study medication.

The patients received one of the following three treatments: heparin (an intravenous bolus injection of 10,000 IU of heparin followed by a continuous intravenous infusion of 15 IU of heparin per kilogram

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*The institutions and investigators participating in the Helvetica trial are listed in the Appendix.

of body weight per hour for 24 hours, with placebo given subcutaneously twice daily for three consecutive days), intravenous hirudin (an intravenous bolus injection of 40 mg of hirudin followed by a continuous intravenous infusion of 0.2 mg of hirudin per kilogram per hour for 24 hours, with placebo given subcutaneously twice daily for three consecutive days), or intravenous and subcutaneous hirudin (an intravenous bolus injection of 40 mg of hirudin followed by a continuous intravenous infusion of 0.2 mg of hirudin per kilogram per hour for 24 hours, with 40 mg of hirudin given subcutaneously twice daily for three consecutive days). If the angioplasty lasted more than one hour, an additional bolus dose of 5000 IU of heparin could be administered at the option of the physician to the patients in the heparin group, or an equivalent amount of placebo could be given to the patients in the hirudin groups. The operators remained blinded to the results of clotting studies, and no adjustment of the rate of infusion of the study medication was allowed. A concomitant dose of aspirin (100 to 500 mg once daily) was given on the day of angioplasty, and this treatment was continued for at least 14 days.

Criteria for Evaluation

Efficacy

The primary end point was event-free survival 30 weeks after angioplasty — that is, the absence of death, nonfatal myocardial infarction, coronary-artery bypass grafting or the use of a "bailout" procedure (e.g., stenting), or second angioplasty at previously dilated sites. Myocardial infarction was diagnosed on the basis of new Q waves (according to the Minnesota Code[13]) or an increase in the serum creatine kinase level to more than twice the upper limit of the normal range, with a concomitant increase in the MB fraction. If a stent was implanted electively after the initial angioplasty (i.e., not as part of a bailout procedure), the implantation was considered equivalent to a second angioplasty. Second angioplasty or bypass surgery needed to be preceded by typical anginal symptoms or, if there were atypical anginal symptoms, by electrocardiographic evidence of myocardial ischemia at rest or during exercise and an angiographically determined stenosis greater than 50 percent by visual inspection.

Secondary end points were as follows: any of a ranked series of clinical events that included death from cardiac causes, nonfatal myocardial infarction, coronary-artery bypass grafting (or the use of a bailout procedure), second angioplasty, and anginal status (according to the classification system of the Canadian Cardiovascular Society[10]) at the 30-week follow-up evaluation; the occurrence of any of these events within 96 hours after the start of the study medication; the minimal luminal diameter of the dilated sites as measured by quantitative coronary angiography at the 26-week follow-up evaluation; and any change in the minimal luminal diameter of dilated sites from immediately after angioplasty to follow-up angiography at 26 weeks.

Safety

Safety was evaluated with regard to bleeding and other complications. Bleeding was classified as major if it was overt and led to a decrease in the hemoglobin level by at least 2 g per deciliter; if it necessitated the transfusion of two or more units of whole blood or packed cells; or if it occurred intracranially, retroperitoneally, or at the site of a major joint.[14] Minor bleeding was defined as overt bleeding that did not meet these criteria.

Angiography and Assessment of Coagulation

For each patient, coronary angiograms were obtained in a standardized fashion immediately before and immediately after angioplasty, and at the six-month follow-up evaluation. The angiograms were analyzed in a core laboratory with the Cardiovascular Angiography Analysis System.[15,16]

Blood samples for the measurement of coagulation were obtained at regular intervals before and after angioplasty. Blood samples for the determination of activated partial-thromboplastin times and levels of prothrombin fragment F_{1+2} (a measure of the generation of thrombin) were obtained separately by atraumatic venipuncture and were analyzed in a central laboratory.

Statistical Analysis

Outcomes were compared in an intention-to-treat analysis, which included all randomized patients in whom coronary angioplasty was attempted. Patients in whom no angioplasty was attempted (i.e., those whose indication for angioplasty changed or disappeared) were excluded from the analysis. A successful procedure was defined as one in which the stenosis was reduced by more than half; in the case of a failed recanalization of a total occlusion, the second lesion treated was considered to be the first site of angioplasty.

The distribution of event-free survival at 30 weeks was calculated according to the method of Kaplan and Meier, and distributions were compared by the Kruskal–Wallis test[17]; for patients with multiple events, the first event was considered. Event rates and rates of bleeding and other complications were compared by the chi-square test.

A linear logistic-regression analysis for ordered categories was performed for the ranked clinical outcomes, with pretreatment with heparin used as a covariate. The most severe event in each patient was considered in the analysis.

The minimal luminal diameters at the dilated sites 26 weeks after angioplasty were compared by analysis of variance, with the mean value for all sites used in cases of angioplasty at multiple sites. All reported P values are two-tailed. Whenever possible, estimates of the magnitude of the treatment effect are provided, with corresponding 95 percent confidence intervals. Relative risks are presented for the combined hirudin groups as compared with the heparin group.

Results

Study Population

A total of 1154 patients were randomized. Of 5686 patients screened, 21 percent were ineligible because they had stable angina, 16 percent for reasons involving logistics, and 11 percent because they had had myocardial infarctions during the previous two weeks. The remaining screened patients (32 percent) were excluded for a wide variety of reasons. Thirteen patients

Table 1. Base-Line Characteristics of the Study Patients According to Group Assignment.*

Characteristic†	Heparin (N=382)	Intravenous Hirudin (N=381)	Intravenous and Subcutaneous Hirudin (N=378)
Male sex	299 (78.3)	300 (78.7)	297 (78.6)
Age (yr)	58.2±8.7	58.7±9.1	58.8±8.9
Weight (kg)	76.0±10.9	75.9±11.1	76.7±10.7
Smoker	104 (27.2)	90 (23.6)	84 (22.2)
Diabetes	44 (11.5)	42 (11.0)	40 (10.6)
Previous MI	148 (38.7)	152 (39.9)	154 (40.7)
Previous CABG	10 (2.6)	8 (2.1)	20 (5.3)
Previous angioplasty	69 (18.1)	69 (18.1)	64 (16.9)
Braunwald class			
I	131 (34.3)	146 (38.3)	139 (36.8)
II	163 (42.7)	160 (42.0)	166 (43.9)
III	88 (23.0)	75 (19.7)	73 (19.3)
Exertional angina — CCS class			
1	7 (1.8)	10 (2.6)	6 (1.6)
2	82 (21.5)	69 (18.1)	66 (17.5)
3	144 (37.7)	163 (42.8)	171 (45.2)
4	102 (26.7)	96 (25.2)	89 (23.5)
IV heparin used at screening	115 (30.1)	110 (28.9)	109 (28.8)
Lesions			
Total no.	482	483	462
Mean no. per patient	1.26	1.27	1.22
Location before angioplasty			
RCA	148 (30.7)	136 (28.2)	139 (30.1)
LAD	230 (47.7)	238 (49.2)	201 (54.5)
LCX	104 (21.6)	109 (22.6)	121 (26.2)
LM	0	0	1 (0.2)

*Plus–minus values are means ±SD. Except as noted, all other values are numbers of patients followed in parentheses by the percentage of the group.

†MI denotes myocardial infarction, CABG coronary-artery bypass graft surgery, CCS Canadian Cardiovascular Society, IV intravenous, RCA right coronary artery, LAD left anterior descending coronary artery, LCX left circumflex coronary artery, and LM left main coronary artery.

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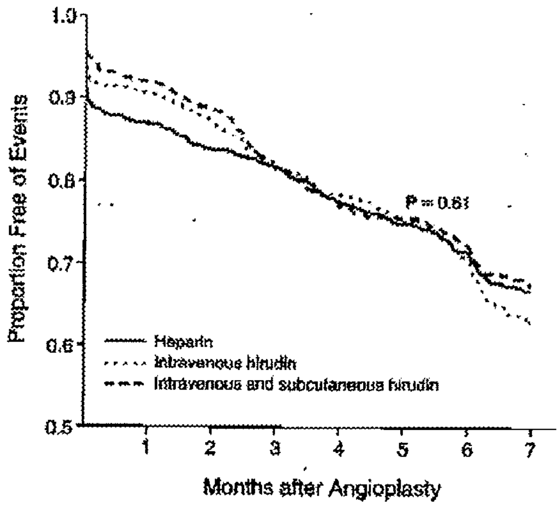

Figure 1. Kaplan–Meier Distribution of Patients without Events in the Intention-to-Treat Analysis (N = 1141).

The groups were compared by the Kruskal–Wallis test.

were not included in the intention-to-treat analysis because no angioplasty was attempted. Among the remaining 1141 patients in whom angioplasty was attempted, 382 were randomly assigned to heparin, 381 to intravenous hirudin, and 378 to intravenous and subcutaneous hirudin. Angioplasty was successful in 91.7 percent; and the results of angiographic follow-up were available for 86.4 percent. Clinical follow-up was complete for all but one patient.

The clinical and angiographic characteristics of the patients at base line are shown in Table 1. The characteristics of the three groups were similar. Almost one third of the patients received intravenous heparin before randomization because of the severity of their unstable angina.

Efficacy

Among the study patients, 125 patients assigned to heparin, 139 assigned to intravenous hirudin, and 121 assigned to intravenous and subcutaneous hirudin reached a primary end point. The distribution of patients free of events is shown in Figure 1. No significant differences were observed among the treatment groups (P = 0.61 by the Kruskal–Wallis test), even after stratification according to pretreatment with heparin.

The incidence of clinical events and angina at 30 weeks is shown in Table 2, with no significant differences among the three groups (P = 0.61). An analysis of subgroups according to whether patients were pretreated with heparin yielded similar results.

The incidence of early events (those occurring in the first 96 hours after angioplasty) is also shown in Table 2. Forty-two patients assigned to heparin, 30 patients assigned to intravenous hirudin, and 21 patients assigned to intravenous and subcutaneous hirudin had such events (relative risk in the combined hirudin groups, 0.61; 95 percent confidence interval, 0.41 to 0.90; P = 0.023). Among the patients pretreated with heparin, there were 20, 7, and 7 events, respectively (combined relative risk with hirudin, 0.37; 95 percent confidence interval, 0.19 to 0.70; P = 0.007). Because these results suggested a particular benefit of hirudin in the most unstable patients (those with Braunwald class III angina), an additional analysis was performed of the 296 patients who had angina at rest during the 48 hours before randomization. The event rate among these patients was 21.6 percent in the heparin group, as compared with 5.3 percent among patients receiving intravenous hirudin and 12.3 percent among patients receiving intravenous and subcutaneous hirudin (combined relative risk with hirudin, 0.41; 95 percent confidence interval, 0.21 to 0.78; P = 0.006).

The imbalance in the number of deaths (Table 2) calls for a description of their exact causes. In the heparin group, three myocardial infarctions and one nonhemorrhagic cerebrovascular accident resulted in death. In the group receiving intravenous hirudin, there was one sudden death. In the group receiving intravenous and subcutaneous hirudin, five patients had fatal myocardial infarctions. In this group there were also two cerebrovascular accidents (one of which was hemorrhagic), one episode of cardiac tamponade, and one sudden death; one patient died of respiratory insufficiency, and one of wound infection and sepsis after bypass surgery.

Linear logistic-regression analysis of ordered categorical data revealed that pretreatment with heparin

Table 2. Clinical Events in the First 96 Hours and the First 30 Weeks in the Intention-to-Treat Analysis.*

Event	Heparin (N = 382)		Intravenous Hirudin (N = 381)		Intravenous and Subcutaneous Hirudin (N = 378)	
	96 hr	30 wk	96 hr	30 wk	96 hr	30 wk
	number (percent)					
Death	2 (0.5)	4 (1.0)	0	1 (0.3)	0	11 (2.9)
Myocardial infarction	16 (4.2)	20 (5.2)	13 (3.4)	19 (5.0)	9 (2.4)	23 (6.1)
Coronary bypass surgery	9 (2.4)	21 (5.5)	6 (1.6)	21 (5.5)	3 (0.8)	25 (6.6)
Bailout procedure	18 (4.7)	18 (4.7)	12 (3.1)	12 (3.1)	8 (2.1)	8 (2.1)
Second angioplasty	13 (3.4)	91 (23.8)	7 (1.8)	109 (28.6)	5 (1.3)	93 (24.6)
Any event	42 (11.0)	125 (32.7)	30 (7.9)	139 (36.5)	21 (5.6)	121 (32.0)
Any exertional angina	—	55 (14.4)	—	71 (18.6)	—	71 (18.8)
No events or symptoms	—	202 (52.9)	—	171 (44.9)	—	186 (49.2)

*At 96 hours, the combined relative risk in the hirudin groups as compared with the heparin group was 0.61 (95 percent confidence interval, 0.41 to 0.90; P = 0.023).

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was significantly associated with worse clinical outcomes at seven months (P=0.03). The type of study medication did not influence outcome in this model.

Base-line angiographic measurements and gains in luminal diameter achieved by angioplasty were similar in the three groups (Table 3). The changes in minimal luminal diameter from immediately after angioplasty to follow-up were also similar (Fig. 2).

Safety

The incidence of bleeding complications is shown in Table 4. No differences with respect to major or minor bleeding were observed among groups. There were three cerebrovascular accidents. One patient receiving intravenous and subcutaneous hirudin was readmitted to the hospital with hemiplegia 14 hours after the final subcutaneous injection; despite surgical evacuation of the intracerebral hematoma causing the condition, the patient died six days after the start of the study treatment. Two intracerebral thrombotic events were observed. One patient (receiving intravenous and subcutaneous hirudin), who presented with symptoms of neurologic deficit one day after discharge from the hospital and who had multiple brain infarctions on computed axial tomography, died five days after the start of the study treatment. Another patient (in the heparin group) presented with massive pulmonary embolism. Paradoxical embolization through a patent foramen ovale caused an extensive, expanding cerebral infarction and led to the patient's death eight days after the start of the study medication.

Anticoagulant Effects

Levels of prothrombin fragment F_{1+2} are shown in Figure 3. The median levels peaked in both hirudin groups at the end of the procedure (from 1.1 nmol per liter at the time of screening to 1.4 nmol per liter in the group receiving intravenous hirudin, and from 1.0 to 1.3 nmol per liter in the group receiving intravenous and subcutaneous hirudin), whereas in the heparin group the levels were slightly reduced (to 0.9 nmol per liter) as compared with those at the time of screening (1.0 nmol per liter). Levels of prothrombin fragment

Table 3. Mean (±SD) Angiographic Measurements in the Intention-to-Treat Analysis of Patients for Whom Follow-up Data Were Available.

Variable	Heparin (N=330)	Intravenous Hirudin (N=341)	Intravenous and Subcutaneous Hirudin (N=315)
		millimeters	
Reference luminal diameter*	2.69±0.51	2.67±0.51	2.70±0.51
Minimal luminal diameter			
Before angioplasty	0.99±0.38	0.97±0.39	1.03±0.35
After angioplasty	1.80±0.37	1.78±0.36	1.82±0.37
At follow-up	1.54±0.59	1.47±0.56	1.56±0.50
Gain	0.81±0.41	0.82±0.44	0.79±0.41
Loss	0.26±0.52	0.32±0.50	0.26±0.45

*As estimated by computer techniques on the basis of the diameters of segments proximal and distal to the site of stenosis.

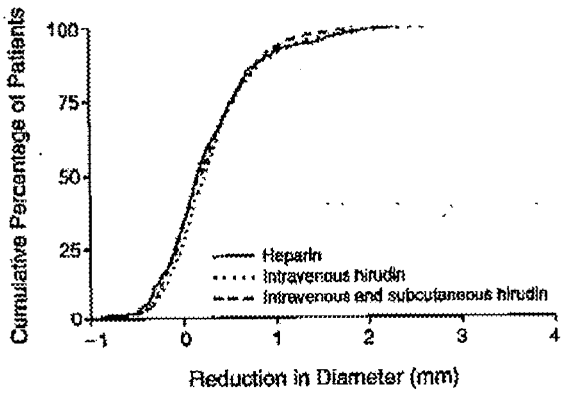

Figure 2. Cumulative Distribution of the Reduction in Minimal Luminal Diameter from Immediately after Angioplasty to Follow-up at Seven Months.

F_{1+2} measured at 24, 96, and 98 hours subsequently returned to the base-line values in all three groups.

Measurements of activated partial-thromboplastin time (Fig. 3) were higher at the end of the procedure in the subjects receiving heparin than in those receiving hirudin, an effect that disappeared after 24 hours. The infusion of hirudin resulted in a more stable effect. Slightly prolonged activated partial-thromboplastin times were observed at 96 hours after angioplasty in the group receiving intravenous and subcutaneous hirudin.

Discussion

Although hirudin was associated with impressive reductions in the rate of major cardiac events in the first 96 hours after angioplasty as compared with heparin, the primary goal of this trial, a reduction in the rate of cardiac events at seven months, was not accomplished. Event-free survival at seven months did not differ among the treatment groups.

At least three other trials using specific antiplatelet drugs have demonstrated beneficial effects on the acute complications of coronary angioplasty without favorably influencing long-term clinical outcomes.[18-20] These findings differ from the results of the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) trial,[21,22] in which the glycoprotein IIb/IIIa receptor was presumed to have been blocked completely and which showed a reduction in early cardiac events that was maintained with longer-term follow-up.

The dosage and duration of treatment in the present trial were chosen as a compromise among safety issues, logistic considerations, and the scientific evidence available when the trial was designed. Primarily, the dosage was based on safety data obtained in healthy volunteers, stable patients undergoing angioplasty, and patients undergoing orthopedic surgery.[23-25] However, the results of assays of prothrombin fragment F_{1+2} immediately after angioplasty suggest that the generation of thrombin was not satisfactorily inhibited in either hirudin group, whereas the dosage of heparin we used resulted in an appropriate decrease in levels of prothrom-

Table 4. Bleeding Complications.

Complication	Heparin (N = 382)	Intravenous Hirudin (N = 381)	Intravenous and Subcutaneous Hirudin (N = 378)
	number (percent) of patients		
Major bleeding			
Overt, with decrease in hemoglobin by ≥2 g/dl	24 (6.2)	18 (4.7)	28 (7.4)
Overt, requiring transfusion of ≥2 units whole blood or packed cells	0	3 (0.8)	0
Intracranial	0	0	1 (0.3)
Retroperitoneal or in a major joint	0	0	0
All	24 (6.2)	21 (5.5)	29 (7.7)
Minor bleeding	43 (11.3)	50 (13.1)	57 (15.1)

bin fragment F_{1+2} at six hours. It can be inferred from these data that the adjustment in the infusion rate — from 0.16 mg per kilogram per hour in the pilot study of patients with stable angina[25] to 0.20 mg per kilogram per hour in the current trial of patients with unstable angina and presumably higher levels of thrombin generation — was too cautious a change in dosage. Zoldhelyi et al.[26] recently reported failing to block the generation of thrombin in their patients despite the presence of a 10,000-fold molar excess of free hirudin over the amount bound in complexes with thrombin. Infusion rates of hirudin in experiments with animals were as much as five times higher than those currently used, a finding that may explain the lack of a long-term effect in the present study.[8,9]

When hirudin was administered subcutaneously in healthy volunteers at a dose of 0.5 mg per kilogram twice daily, the activated partial-thromboplastin time 12 hours after the first injection was subtherapeutic,[23] and it may be inferred that the inhibition of the conversion of prothrombin was also inadequate in the first three days of the trial. A putative explanation for the apparent paradox by which the early outcome is improved although there is less appropriate control of thrombin may be that the dosage used was not sufficient to produce an adequate level of anticoagulation, but was sufficient to limit the thrombin-mediated aggregation and activation of platelets, causing effects similar to those observed over the short term in the EPIC trial.[5,21,22]

The optimal duration of treatment is unknown, even in animal models. Conflicting findings about the time course of thrombogenicity in the injured vessel wall have been reported.[27-30] In this study we decided to maintain our patients at effective levels of antithrombin activity as long as possible. Since ethical considerations necessitated monitoring the patients' safety in the hospital during the subcutaneous injections of hirudin, a reasonable compromise between the duration of hirudin administration and logistic considerations of the trial was presumably achieved by administering the

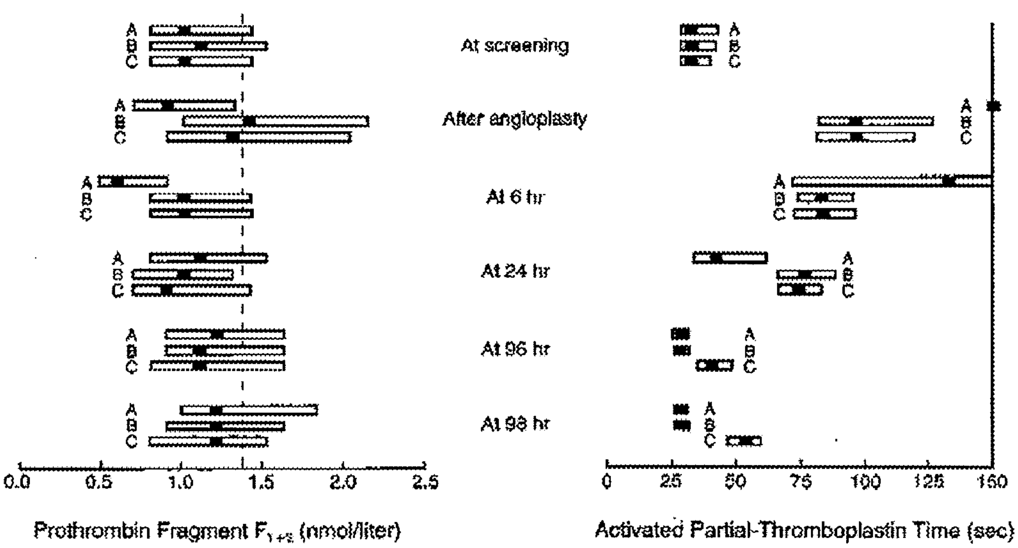

Figure 3. Levels of Prothrombin Fragment F_{1+2} and Activated Partial-Thromboplastin Times in the Three Study Groups at Various Times before and after Angioplasty.

A denotes the group receiving heparin, B the group receiving intravenous hirudin, and C the group receiving intravenous and subcutaneous hirudin. The solid area inside each box indicates the median value, and the left and right margins of the box indicate the upper limits of the first and third quartiles, respectively.

In the left-hand panel, the dotted vertical line indicates the upper limit of the normal level of prothrombin fragment F_{1+2} (1.4 nmol per liter). Heparin tended to control the generation of thrombin better than hirudin both immediately after angioplasty and six hours after the start of the infusion.

In the right-hand panel, the activated partial-thromboplastin time was measured up to a maximum of 150 seconds. Over the first 24 hours this value was more than double the base-line value in the hirudin-treated groups, whereas in the heparin-treated group it returned almost to the base-line level.

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drug intravenously for 24 hours and subcutaneously for three consecutive days.

A clearly beneficial effect of hirudin on platelet aggregation and thrombus formation was indicated by the prevention of acute ischemic events early after angioplasty. The failure of hirudin in this trial to alter longer-term outcomes indicates either that thrombin generation and thrombus formation in the period immediately after angioplasty may be less important in the process of restenosis than was previously believed or that complete reversal of the thrombogenicity of the injured vessel wall was not achieved or requires more time. Whether the large decrease in major events observed with hirudin early after the infusion can be translated to an improved long-term outcome with prolonged subcutaneous administration of hirudin deserves further study.

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Appendix

The following institutions and investigators participated in the Helvetica (Hirudin in a European Trial versus Heparin in the Prevention of Restenosis after PTCA) trial. The number of patients enrolled at each center is given in parentheses, followed by an asterisk when all patients in the cardiac catheterization laboratory at a center were screened and the results entered in a logbook.

Medizinische Klinik III, Heidelberg, Germany (66)* — C. Bode, G. Schuler, S. Abed, H. Baumann; Universitätsklinik Rudolf Virchow, Berlin (66)* — W. Rutsch, G. Brunckhurst, N. Kokott; Medizinische Universitätsklinik, Kiel, Germany (66)* — R. Simon, M. Lins, G. Herrmann; Onze Lieve Vrouwe Gasthuis, Amsterdam (60)* — G.J. Laarman, F. Kiemeneij, H. Swart; Medisch Centrum de Klokkenberg, Breda, the Netherlands (54)* — A. van den Bos, M. Quarles van Ufford, U. Chin-Kon-Sung, G. Uytdehaag; Academisch Ziekenhuis Groningen, Groningen, the Netherlands (54) — R. van Dijk, P. Den Heyer, L. Drok, J. Klein; Istituto Apparato Cardiovascolare, Bologna, Italy (54)* — A. Marzocchi, G. Piovaccari, C. Marrozinni, E. Cere; Academisch Ziekenhuis Dijkzigt, Rotterdam, the Netherlands (54)* — P. Serruys, P. de Feyter, V. Umans, J. Herrman; Ospedali Riuniti, Bergamo, Italy (53)* — G. Guagliumi, O. Valsecchi, A. Casari, A. Piti', A. Tasca; Medizinische Universitätsklinik, Freiburg, Germany (52)* — A. Zeiher, H. Wollschläger, V. Schächinger; Hospital General Gregorio Maranon, Madrid (48)* — J. Delcan Dominguez, E. Garcia, J. Joriano, J. Elizaga; Sahlgrenska Hospital, Göteborg, Sweden (48)* — H. Emanuelsson, P. Albertsson, P. Hardhammar, L. Ekström; Hospital Clinico San Carlos, Madrid (48)* — C. Macaya, F. Alfonso, R. Hernandez, A. Iniguez; CHU Sart Tilman, Liège, Belgium (44)* — V. Legrand, M. Bellekens, P. Marcelle, P. Doneux; Ospedale di Circolo, Varese, Italy (36)* — G. Binaghi, S. Repetto, E. Verna, B. Castiglioni; Hospital Marques de Valdecilla, Santander, Spain (30)* — T. Colman, J. Zueco, A. Figueroa; U.C.L. Saint-Luc, Brussels, Belgium (30)* — C. Hanet, W. Wijns, J. Cosyns, X. Michel; Ospedale Maggiore, Trieste, Italy (30)* — S. Klugmann, E. Della Grazia, L. Barbieri; Hôpital Universitaire de Mont-Godinne, Yvoir, Belgium (30)* — E. Schroeder, P. Chenu, D. Grolaux; CHR Nancy, Vandoeuvre-les-Nancy, France (26)* — N. Danchin, Y. Juilliere, F. Cherrier, C. Ketrani; Onze Lieve Vrouwziekenhuis, Aalst, Belgium (26)* — G. Heyndrickx, B. de Bruyne, M. Goethals, P. Goemare; Franz Volhard Klinik, Berlin-Buch, Germany (24)* — D. Gulba, G. Claus, S. Hauck; Centre Cardiologique du Nord, Saint Denis, France (24)* — M.-C. Morice, T. Royer, B. Glatt, E. Rosenblatt; Ziekenhuis de Weezenlanden, Zwolle, the Netherlands (24) — F. Zijlstra, H. Suryapranata, H. Schoenmaker, G. Velsink; Hospital Clinic i Provincial, Barcelona, Spain (23)* — A. Betriu, A. Serra, G. Sanz, M. Heras; Catharina Ziekenhuis, Eindhoven, the Netherlands (18)* — J. Bonnier, N. Pijls, M. el Gamal, S. Rouffel; Ospedale Niguarda, Milan, Italy (18)* — L. Campolo; Policlinico San Matteo, Pavia, Italy (18)* — G. Specchia, S. de Servi, F. Marizco; Centre Chirurgical Marie Lannelongue, Les Plessis Robinson, France (15)* — B. Lancelin, B. Chevalier, F. Guyon, F. Philippe; CHRU Rouen Hôpital, Rouen, France (15)* — B. Letac, H. Eltchaninoff, R. Koning, A. Cribier.

Steering Committee: P.W. Serruys (chairman), A. Betriu, F. Camerini (Ospedale Maggiore, Trieste, Italy), N. Danchin (Hôpital Brabois, Vandoeuvre-les-Nancy, France), H. Emanuelsson, W. Rutsch, A. van den Bos, P. Close, J.W. Deckers, R. Kerry (Pharma Division, Ciba-Geigy Ltd., Basel, Switzerland), J. Rijnierse (Ciba-Geigy, Arnhem, the Netherlands), P. Peerboom (Cardialysis, Rotterdam), V. Umans. *Sponsor* (Ciba-Geigy, Basel, Switzerland): P. Close, R. Kerry, P. Kobi. *Angiographic Core Laboratory* (Cardialysis, Rotterdam): L. Rodenburg, P.F. Peerboom, E. Nibbering, J. Pameijer, J.P.R. Herrman, V.A.W.M. Umans, J.W. Deckers. *Data Coordinating and Analysis Center:* Ciba-Geigy — P. Close, R. Kerry, P. Kobi, D. Bach, E. Grundl; Department of Clinical Epidemiology and Biostatistics, Cardialysis — R. Melkert. *Hemostasis Core Laboratory* (Department of Hemostasis and Thrombosis, Academic Medical Center, Amsterdam) — H. Büller. *Safety Committee:* K. Fox (chairman), H. Büller, D. Chamberlain (Royal Sussex County Hospital, Brighton, United Kingdom), Z. Pelikan (Medisch Centrum de Klokkenberg, Breda, the Netherlands), J. Tijssen (Academic Medical Center, Amsterdam). *Critical Events Committee:* H. Schmutzler (chairman) (Universitätsklinik Rudolf Virchow, Berlin), G. Heyndrickx, A. Zeiher, G. Specchia. *Angiography Committee:* R. Simon (chairman), V. Legrand, G.J. Laarman, H. Suryapranata. *Study directors:* J.W. Deckers, P. Close.

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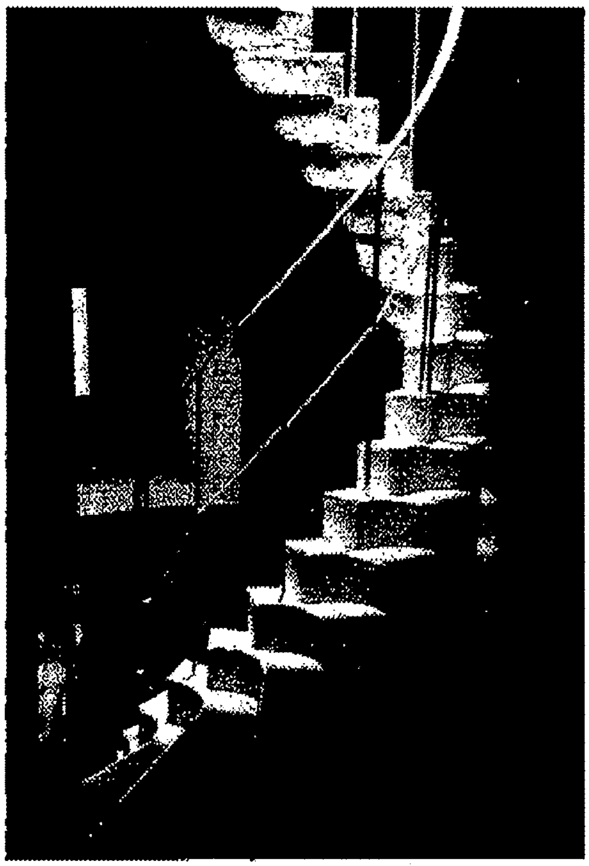

Stairway, Palazzo Ducale GARY S. REITER, M.D.

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Inter Partes Reexamination No. 95/001,096
Declaration of Campbell Rogers, M.D.
Exhibit 98

EuroIntervention

A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial

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This study was sponsored by Advanced Cardiovascular Systems, an Abbott Vascular Company
All authors declare no conflict of interest

KEYWORDS
Stent, eluting stent, everolimus, randomised trial

Abstract

Background: Everolimus has been successfully tested in humans using both an erodable and a durable polymer in small previous studies.

Methods: This single blind multi-centre non-inferiority randomised (3:1) controlled trial evaluated the safety and performance of the XIENCE V Everolimus Eluting Coronary Stent System (XIENCE V EECSS) versus the TAXUS Paclitaxel Eluting Coronary Stent System (TAXUS® PECSS) in the treatment of patients with a maximum of two *de novo* native coronary artery lesions located in two different epicardial vessels. Three hundred patients with evidence of myocardial ischaemia were allocated to stent implantation with an everolimus-eluting stent (n=223) or a paclitaxel-eluting stent (n=77). Suitable lesions had a diameter stenosis of ≤50-99%, a length of ≤28 mm, and a reference vessel diameter between 2.5 mm and 4.25 mm. The primary endpoint was in-stent late loss (LL) at 180 days. Percentage in-stent volume obstruction (%VO) was measured by intravascular ultrasound (IVUS) in a subset of 152 patients. Clinical secondary endpoints included ischaemia driven major adverse cardiac events (ID-MACE) at 180 days.

Results: At 6 months, the in-stent LL was 0.11±0.27 mm in the everolimus-eluting stent arm, as compared to 0.36±0.39 mm in the paclitaxel-eluting stent arm ($p<0.0001$). Percentage VO in the everolimus-eluting stent arm was 2.5±4.7% versus 7.4±7.0% in the paclitaxel-eluting stent arm ($p<0.0001$). Hierarchical MACE was 2.7% (6/222) in the everolimus-eluting stent arm vs. 6.5% (5/77) in the paclitaxel-eluting stent arm.

Conclusion: This non-inferiority randomised trial not only met its primary endpoint, but also demonstrated the superiority of the everolimus-eluting stent over the paclitaxel-eluting stent in terms of in-stent late loss.

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Introduction

Recent studies that have evaluated the local application of anti-proliferative drugs (sirolimus and paclitaxel) for the prevention of restenosis via a stent delivery system have shown that these therapies successfully inhibit the development of neointimal hyperplasia and reduce restenosis and associated clinical events.[1,2]

Everolimus is an effective anti-proliferative agent that inhibits growth factor-stimulated cell proliferation by causing cell cycle arrest in the late G1 stage in the cell cycle.[3]

The feasibility of using everolimus on a drug-eluting stent was demonstrated in the earlier FUTURE I[4,5] and FUTURE II[6,7] studies and more recently in the SPIRIT FIRST[8] study, using the everolimus-eluting stent. The SPIRIT FIRST study (N=60) was a multi-centre, single blinded controlled study conducted to assess the feasibility and efficacy of the everolimus-eluting stent in the treatment of patients with *de novo* native coronary artery lesions compared to the metallic, uncoated MULTI-LINK VISION RX Coronary Stent. This feasibility trial showed clinical safety and the angiographic in-stent Late Loss (LL) observed was 0.10 mm, a reduction of 88% relative to the bare metal stent at six months and an in-stent LL of 0.24 mm at 12 months, which was a reduction of 71%.[8,9]

The SPIRIT II trial is a continuation of the assessment of the safety and performance of the XIENCE V everolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in the treatment of patients with a maximum of two *de novo* native coronary artery lesions.

Methods

Patient selection

This prospective, randomised (3:1) single-blind, parallel two-arm trial was performed at 28 centres in Europe, India and New Zealand and enrolled patients from July 2005 to November 2005. It was approved by the ethics committee at each participating institution, and all patients gave written informed consent.

Patients were eligible for the study if they were older than 18 years and had evidence of myocardial ischaemia. The patient could have a maximum of two *de novo* native coronary artery lesions, which had to be located in different major epicardial vessels. The *de novo* target lesion(s) had to have a reference vessel diameter between 2.5 mm and 4.25 mm by visual estimation, a target lesion length ≤28 mm, a visually estimated stenosis between 50-99% of the luminal diameter, and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of 1 or more. Patients were not eligible for enrolment if they had known diagnosis of acute myocardial infarction three days prior to the baseline procedure, a left ventricular ejection fraction of less than 30%, were awaiting a heart transplant, or had a known hypersensitivity or contraindication to aspirin, heparin, bivalirudin, clopidogrel or ticlopidine, cobalt, chromium, nickel, tungsten, everolimus, paclitaxel, acrylic and fluoro polymers or contrast sensitivity that could not be adequately pre-medicated. Additionally, patients having target lesion(s) with an aorto-ostial or left main location, a lesion located within 2 mm of the origin of the left anterior descending- or left circumflex, heavy calcification, or a visible thrombus within the target vessel were also excluded from the trial.

The everolimus-eluting stent

The XIENCE V Everolimus Eluting Coronary Stent System (EECSS) (Advanced Cardiovascular Systems, an Abbott Vascular Company, IL, USA) is comprised of the ACS MULTI-LINK VISION Stent and delivery system, and a drug eluting coating. The ACS MULTI-LINK VISION Stent is a balloon expandable stent, which consists of serpentine rings connected by links fabricated from a single piece of medical grade L-605 cobalt chromium alloy.

Everolimus is blended in a non-erodable polymer, coated over another non-erodable polymer primer layer. The coating comprises acrylic and fluoro polymers, both approved for use in blood contacting applications. This layer of everolimus-polymer matrix with a thickness of 5-6 microns is applied to the surface of the stent and is loaded with 100 micrograms of everolimus per square centimetre of stent surface area with no topcoat polymer layer. The stent is designed to release approximately 80% of the drug within 30 days after implantation.

Everolimus (Certican®, Novartis Corporation) has been evaluated in clinical trials in the US and Europe for use as an immunosuppressant following cardiac and renal transplantation.[10] Everolimus has received market approval in the European Union and the XIENCE V EECSS has received CE mark in the European Union.

Study procedure

Following the confirmation of angiographic inclusion and exclusion criteria prior to the procedure, patients were enrolled through a telephone randomisation service and assigned in a 3:1 ratio to either an everolimus-eluting stent or a paclitaxel-eluting stent. The stents were available in lengths of 8, 18 and 28 mm, and diameters of 2.5, 3.0, 3.5 and 4.0 mm. Lesion lengths greater than 22 or less than or equal to 28 mm were to be covered by 2 stents; twice an 18 mm stent, or a 28 mm and an 8 mm stent.

Lesions were treated using standard interventional techniques with mandatory pre-dilatation and stent implantation at a pressure not exceeding the burst pressure rate. Due to packaging differences, physicians were not blinded to the device. Post-dilatation was left to the discretion of the physician, however, if performed, it was only to be done with balloons sized to fit within the boundaries of the stent. In the event of a bailout procedure and additional stent requirement, the stent had to be one from the same arm as the first implanted stent. IVUS was performed in a subset of 152 consecutive patients enrolled in pre-selected centres, after angiographically optimal stent placement had been obtained, and was repeated if additional post-dilatation was performed to optimise stent apposition and/or deployment.

Peri-procedural pharmaceutical treatment was administrated according to standard hospital practice. Either unfractionated heparin or bivalirudin could be used for procedural anticoagulation. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the physician. All patients enrolled into the study were pre-treated with a loading dose of 300 mg of clopidogrel and maintained on 75 mg of clopidogrel daily for a minimum of 6 months and ≥75 mg of aspirin daily for a minimum of one year following the procedure. Clinical device success was defined as a successful delivery and

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deployment of the first inserted study stent (in overlapping stent setting a successful delivery and deployment of the first and second study stent) at the intended target lesion with attainment of final residual stenosis of 50% of the target lesion by QCA (by visual estimation if QCA unavailable). Bailout patients were included as clinical device success only if the above criteria for clinical device success were met.

Clinical procedure success included the previous criteria of clinical device success, but with the addition of any study stent or other stent devices and required the absence of ID-MACE during the hospital stay. In dual lesion setting both lesions had to meet clinical procedure success.

Follow-up

Patients were evaluated at 30 and 180 days. Further evaluations will be performed at 270 days, 1 and 2 year(s) and will form the subject of additional reports. At outpatient visits, patients were asked specific questions about the interim development of angina or the occurrence of MACE. Angiographic follow-up for all patients and IVUS in a subset of 152 consecutive patients (enrolled at selected centres) were performed at 180 days, and both investigations will be repeated at 2 years for this subset of patients. Prior to performing a follow-up angiogram, the physician was required to record prospectively in the eCRF whether a revascularisation (if required) was clinically indicated – defined as the presence of ischaemic symptoms and/or a positive functional ischaemia study.

Quantitative coronary angiography evaluation

Quantitative coronary angiography was performed using the CAAS II analysis system (Pie Medical BV, Maastricht, Netherlands).[11] In each patient, the stented segment and the peri-stent segments (defined by a length of 5 mm proximal and distal to the stent edge) were analysed. The following QCA parameters were computed: minimal luminal diameter (MLD), reference vessel diameter (RVD) obtained by an interpolated method, and percentage diameter stenosis (%DS). Binary restenosis (BR) was defined in every segment as diameter stenosis ≥50% at follow-up. Late loss (LL) was defined as the difference between MLD post-procedure and MLD at follow-up.

Intravascular ultrasound analysis

Post-procedure and follow-up stented vessel segments were examined with mechanical or phased array intravascular ultrasound (Eagle-eye™ Volcano, Atlantis™, Boston Scientific) using automated pull-back at 0.5 mm per second. The coronary segment beginning 5 mm distal to and extending 5 mm proximal to the stented segment was examined. A computer-based contour detection program was used for automated 3-D reconstruction of the stented and adjacent segments. The lumen, stent boundaries and external elastic membrane (vessel boundaries) were detected using a minimum cost algorithm.[12] The stent volume (SV) and lumen volume (LV) were calculated according to the Simpson's rule.[13] The intrastent neointimal volume was calculated as the difference between SV and LV. The percentage obstruction of the stent volume was calculated as intrastent neointimal volume/stent volume*100. Feasibility, reproducibility and inter- and intra-observer variability of this system have been validated *in vitro* and *in vivo*.[13] Incomplete apposition was defined as one or more stent struts separated from the vessel wall with evidence of blood speckles behind the strut on ultrasound, while late-acquired incomplete apposition was defined as incomplete apposition of the stent at follow-up which was not present post-procedure.[14-16]

Study endpoints

The primary endpoint was angiographic in-stent LL, as determined by quantitative angiography, based on an "analysis lesion": one randomly selected lesion per patient to avoid inter-lesion dependence[20]. Secondary endpoints (QCA and IVUS) at 180 days and 2 years (subset of 152 consecutive patients enrolled at selected centres) included the in-stent, in-segment, proximal and distal LL; in-stent and in-segment angiographic binary restenosis rate and %DS; in-stent percentage volume obstruction (%VO) and plaque behind the stent; and persisting and late-acquired incomplete stent apposition, aneurysm, thrombosis and persisting dissection. In-stent was defined as within the margins of the stent while in-segment was defined as located within the margins of the stent and 5 mm proximal or distal to the stent. Late loss was calculated as the difference between the post-procedure and follow-up minimum luminal diameters.

Secondary clinical endpoints included Ischaemia-Driven MACE (comprised of cardiac death, myocardial infarction and Ischaemia-Driven Target Lesion Revascularisation [ID-TLR]) either by CABG or PCI, evaluated at 30, 180 and 270 days, 1 and 2 year(s) after the index procedure and acute success including clinical device and clinical procedure success.

All deaths that could not be clearly attributed to another cause were considered cardiac deaths.

A non-Q-wave myocardial infarction was defined as a typical rise and fall of CK-MB* with at least one of the following: ischaemic symptoms, ECG changes indicative of ischaemia (ST segment elevation or depression) or coronary artery intervention. (*if non-procedural/spontaneous MI, CK-MB ≥2 times upper limit of normal; if post PCI, CK-MB ≥3 times upper limit of normal; if post CABG, CK-MB ≥5 times upper limit of normal).

ID-TLR was defined as a revascularisation at the target lesion associated with any of the following: non-invasive positive functional ischaemia study (e.g. exercise testing or equivalent tests) or invasive positive functional ischaemia study (e.g. Fractional Flow Reserve [FFR] or Coronary Flow Reserve [CFR]); ischaemic symptoms and an angiographic%DS ≥50% by on-line quantitative coronary angiography (QCA);%DS ≥70% by on-line QCA without either ischaemic symptoms or a positive functional study. The investigator assessment could potentially be overruled by QCA off-line from the core laboratory.

Stent thrombosis, categorised as acute (≤1 day), subacute (> 1 day ≤30 days) and late (> 30 days), was defined as any of the following: in the presence of angiography, clinical presentation of acute coronary syndrome[17] with angiographic evidence of stent thrombosis. In the absence of angiography: cardiac death or acute MI in the territory of the stented vessel/vessels; AMI that could not be distinctly attributed to a non-target vessel during the Clinical Events Committee adju-

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dication was considered in the composite for stent thrombosis. The endpoints were adjudicated by an independent clinical events committee (appendix I). In addition, a data and safety monitoring board that was not affiliated with the study reviewed the data to identify any safety issues related to the conduct of the trial (appendix I).

Statistical analysis

The primary endpoint and all trial endpoints were analysed on both the intent-to-treat and per-treatment evaluable populations, the latter of which consisted of patients who had no major protocol deviations, as evaluated in a blinded manner.

The sample size for the study was determined based on the primary endpoint of in-stent LL at 180 days and on the following assumptions: one-tailed non-inferiority test, overall α equals 0.05, randomisation ratio was 3 (everolimus arm):1 (paclitaxel arm), the true mean in-stent late loss was assumed to be 0.32 mm in the XIENCE V arm and 0.39 mm in the TAXUS arm, a non-inferiority margin delta (δ) of 0.16 mm and the group sequential design was based on the method described in Reboussin, et al. indexed by O'Brien & Fleming boundary.[18,19] Four interim analyses were planned and the final analysis was performed at the 0.0448 adjusted significance level. Given the above assumptions, analysing 180 patients in the test arm and 60 patients in the active control arm provides more than 91% power. In order to account for drop-outs and to ensure enough angiographic data, approximately 300 patients had to be enrolled of which 225 in the everolimus arm and 75 in the paclitaxel arm.

In this paper binary variables were compared using the Fisher's exact test. Continuous variables were compared using Wilcoxon two-sample test. The hypothesis testing for the primary endpoint was performed using a one-sided non-inferiority test with asymptotic test statistic. If non-inferiority would be shown, superiority analysis was planned using a two-sided t-test at the 5% alpha level. Due to inclusion of dual vessel/lesion treatment, as a secondary analysis, a repeated measures analysis using all target lesions was performed and compared with the analysis using 'analysis lesion'. Final 6-month results are presented in this manuscript.

Results

Patient characteristics

Between July 2005 and November 2005, 223 patients were randomly assigned to receive the everolimus eluting stent, and 77 were assigned to receive the paclitaxel eluting stent. As defined in the protocol, all results are presented for the intent-to-treat population; 222 patients in the everolimus arm, and 77 patients in the paclitaxel arm (Figure 1). In the everolimus arm there was one withdrawal prior to 180 days. The two arms were similar with respect to baseline clinical variables examined in Table 1.

Procedural characteristics

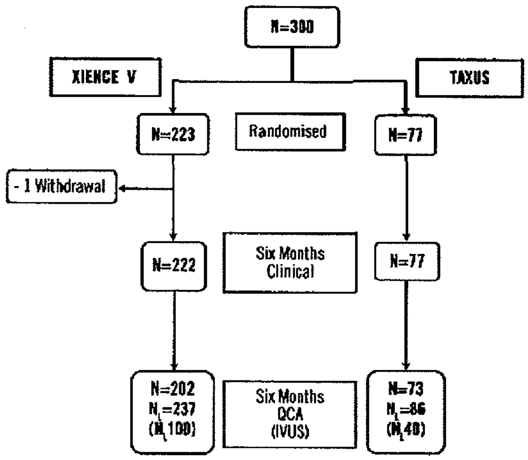
The lesions in the two arms were treated similarly with the use of conventional techniques. Per patient, 1.4 study stents were implanted in the everolimus arm and 1.3 in the paclitaxel arm. Mean stent

Table 1. Baseline characteristics of the per-treatment patient population and of each treatment arm.*

	Everolimus stent (n=223)	Paclitaxel stent (n=77)	All patients (n=300)
Age(yrs)	62±10	62±9	62±10
Male gender (%)	71	79	73
Current Smokers (%)	32	30	31
Diabetes (%)	23	24	23
Hypertension Requiring Medication (%)	67	65	67
Hyperlipidaemia Requiring Medication (%)	69	75	70
Prior TV Intervention (%)	4	4	4
Prior MI (%)	35	25	32
Stable Angina (%)	62	62	62
Unstable Angina (%)	27	32	28
Target Vessel (%)	N_L=260**	N_L=91**	N_L=351**
Left Anterior Descending	41	47	42
Left Circumflex	29	19	26
Right Coronary Artery	30	34	31
AHA / ACC #			
Lesion Class (%)			
A	1	0	1
B1	21	20	21
B2	65	67	66
C	13	13	13
Reference Vessel Diameter (mm±SD)***	2.70±0.52	2.82±0.58	2.73±0.54
Lesion Length (mm±SD)	13.0±5.7	13.2±6.4	13.0±5.9

* There were no significant differences between the treatment arms; ** N_L = lesion number; *** RVD pre p=0.099; difference: −0.12 [−0.26;0.02]
# AHA/ACC = American Heart Association/American College of Cardiology

QCA, quantitative coronary angiography;
IVUS, intravascular ultrasound



One patient crossed over from the XIENCE V to TAXUS arm but is still counted in the XIENCE V arm (Intent to Treat)

Figure 1. Flowchart of patients.

deployment pressure was 15 atmospheres in each arm and post dilatation was performed in 39% of lesions in the everolimus arm and 27% of lesions in the paclitaxel arm. Bail out study stents were used in 5.4% of lesions in the everolimus arm and 4.5% of lesions in the paclitaxel arm. Both arms had similar rates of clinical device success 98.8% (256/259) for the everolimus arm vs. 98.9% (89/90) for the paclitaxel arm and they did not differ significantly with respect to the rate of clinical procedure success 99.1% (221/223) in the everolimus arm and 97.4% (75/77) in the paclitaxel arm.

Quantitative coronary angiography analysis

Angiographic data at 180 days was available for 275 analysable patients (92%). Pre-procedure, the RVD of the everolimus arm tended to be smaller than in the paclitaxel arm without reaching statistical significance. Post-procedure, this difference became significant at 5% alpha. The significantly smaller MLD pre-procedure and a slightly smaller acute gain in the everolimus arm resulted in a statistically significant difference in post-procedure MLD (2.49mm vs. 2.62 mm; –0.13 [–0.24;–0.03]) (Table 2). At 180 days, the mean in-stent LL (analysis lesion, intent-to-treat population) was significantly lower for the everolimus arm compared to the paclitaxel arm, 0.11±0.27mm versus 0.36±0.39mm (non-inferiority p<0.0001, superiority p<0.0001). (Figure 2)

For the per lesion analysis, the mean in-stent MLD,%DS and BR rate were 2.38±0.50 mm, 16±10% and 1.3% (3/237), respectively in the everolimus-eluting arm, as compared to 2.27±0.54 mm, 21±12%, and 3.5% (3/86) in the control arm. Figure 2 shows the cumulative distribution frequency curve of diameter stenosis at 180 days in each treatment arm. Table 2 shows the results of sub-segmental quantitative angiographic analysis for both treatment arms. The in-segment, proximal, and distal LL were non-statistically different between the two arms. However, the in-segment %DS was significantly lower in the everolimus arm.

Table 2. Results of sub-segmental quantitative coronary angiographic analysis

	Proximal Edge			In-Stent			Distal Edge			In-Segment Analysis		
	[illegible]	[illegible]	P-value	[illegible]	[illegible]	P-value	[illegible]	[illegible]	P-value	[illegible]	[illegible]	P-value
Reference vessel diameter (mm)												
Pre-procedure	na	na		2.70±0.52	2.82±0.58	0.099	na	na		na	na	
Post- procedure	na	na		2.86±0.43	3.00±0.48	0.019	na	na		2.78±0.47	2.89±0.49	0.049
At 6 months	na	na		2.81±0.47	2.87±0.51	0.315	na	na		2.75±0.49	2.85±0.53	0.061
MLD/LL (mm)												
MLD pre-procedure	na	na		1.06±0.42	1.14±0.36	0.032	na	na		na	na	
Acute Gain	na	na		1.43±0.43	1.48±0.38	0.232	na	na		na	na	
MLD Post- procedure	2.60±0.53	2.73±0.68	0.155	2.49±0.40	2.62±0.45	0.031	2.26±0.50	2.31±0.57	0.550	2.15±0.44	2.22±0.53	0.269
LL at 6 months*	na	na		0.11±0.27	0.36±0.39	<0.0001**	na	na		na	na	
LL at 6 months***	0.12±0.39	0.16±0.40	0.699	0.12±0.29	0.37±0.38	<0.0001	0.02±0.35	-0.01±0.37	0.650	0.07±0.33	0.15±0.38	0.084
MLD at 6 months	2.50±0.60	2.59±0.65	0.328	2.38±0.50	2.27±0.54	0.153	2.26±0.59	2.33±0.58	0.354	2.10±0.51	2.08±0.54	0.838
Diameter Stenosis (%)****												
Pre-procedure	na	na		61±12	59±10	0.173	na	na		na	na	
Post-procedure	10±6	10±7	0.710	13±6	13±6	0.486	12±5	12±6	0.164	23±9	23±11	0.779
At 6 months	11±9	10±7	0.694	16±10	21±12	<0.0001	12±8	12±7	0.398	24±12	27±13	0.013
Binary Restenosis (%)****												
At 6 months	0.4	0.0	1.000	1.3	3.5	0.194	0.4	0.0	1.000	3.4	5.8	0.343

* Analysis lesion intent to treat (primary endpoint in-stent late loss); ** P value for both non-inferiority (delta 0.16mm) and superiority; *** Per lesion analysis;
**** In-stent and in-segment based on interpolated RVD; proximal and distal based on mean edge diameter; MLD: Minimal Luminal Diameter; LL: Late Loss; N_L: lesion number at follow-up.

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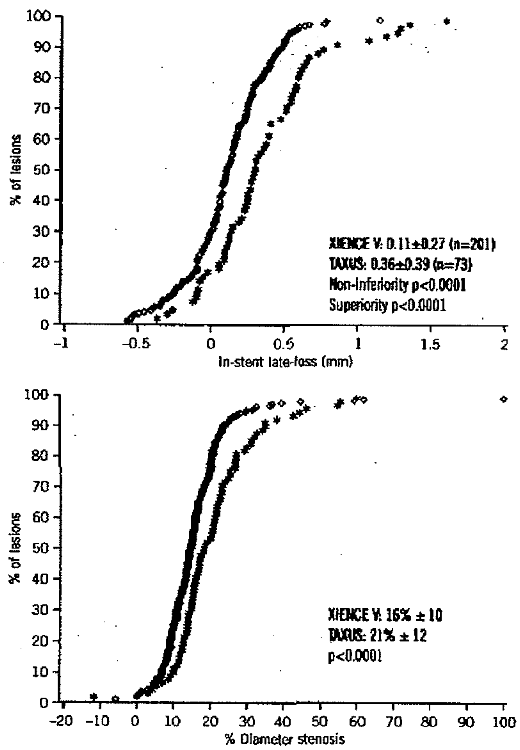

Figure 2. Cumulative frequency of in-stent late loss (analysis lesion) and in-stent percentage diameter stenosis at follow-up (all lesions).

Intravascular ultrasound evaluation

At 180-days, intravascular ultrasound evaluation showed no significant differences between the two arms with respect to the volume of the stent or the lumen volume (Table 3). However, there was a significant difference in vessel volume which reflects the small imbalance in vessel size seen at baseline between the everolimus and paclitaxel arms and the nominal stent volume (calculation based on the nominal stent diameter and stent length) which was 186 mm^3 in the paclitaxel arm and 173 mm^3 in the everolimus arm. Significantly less neointimal hyperplasia was observed in the everolimus-eluting stent arm compared to the paclitaxel-eluting stent arm (4±7 mm^3 vs. 14±16 mm^3, $p<0.001$) and similarly, significantly less %VO, (2.5±4.7% vs. 7.4±7.0%, $p<0.001$). Figure 3 shows the cumulative frequency distribution curve of %VO.

Of the seven patients in the everolimus arm in which post-procedure stent malapposition was observed, three were persisting, three were resolved and one was not evaluable at 180 days. In the paclitaxel arm both cases of stent malapposition observed post-procedure were resolved at 180 days. There were no cases of late acquired stent malapposition in either arms.

Table 3. IVUS Measurements at 6 months follow-up

	[illegible]	Paclitaxel stent (N=[illegible])	[illegible]
Vessel volume (mm^3)	340±160	408±208	0.030
Stent volume (mm^3)	167±85	192±97	0.157
In-stent neo-intima volume (mm^3)	4±7	14±16	<0.001
Lumen volume (mm^3)	164±85	178±92	0.409
In-stent volume obstruction (%) ‡	2.5±4.7	7.4±7.0	<0.001

‡ In-stent volume obstruction=100*(In-stent neo-intima volume/Stent volume)

Major adverse cardiac events

Major adverse cardiac events (MACE) are listed in Table 4. Hierarchically, for the intent-to-treat population in the everolimus

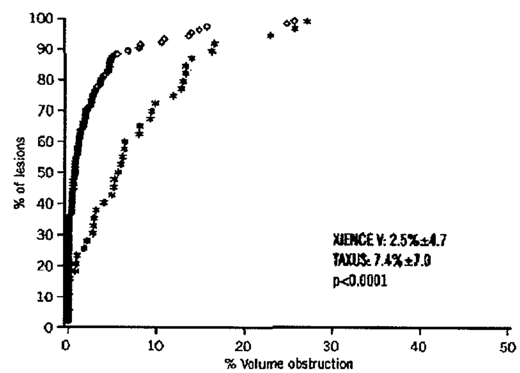

Figure 3. Cumulative curve of in-stent percentage volume obstruction.

Table 4. Major adverse cardiac events and stent thrombosis events at 6 months in intent to treat population

	Everolimus Stent n=222	%	Paclitaxel stent n=77	%
Hierarchical events				
Cardiac death	0	0	1	1.3
Myocardial infarction				
Q-wave	0	0	0	0
Non-Q-wave	2	0.9	2	2.6
Re-intervention				
ID-TLR-CABG	0	0	0	0
ID-TLR-PCI	4	1.8	2	2.6
Major adverse cardiac events	6	2.7	5	6.5
Non-hierarchical revascularisations				
ID-TLR	4	1.8	3	3.9
Non-ID-TLR	2	0.9	2	2.6
All TLR	6	2.7	5	6.5
Stent thrombosis	N	%	N	%
Acute	0	0	0	0
Sub-acute	0	0	0	0
Late	1*	0.5	1#	1.3

*Everolimus patient: at 53 days, dual antiplatelet therapy ongoing
#Paclitaxel patient: at 56 days, fainting, asystole, resuscitation and death, dual antiplatelet therapy ongoing
ID=Ischaemia Driven

arm two (0.9%) non-fatal non-Q wave MIs and four (1.8%) ID-TLRs by PCI were identified compared to one cardiac death (1.3%), two (2.6%) non-fatal non-Q wave MIs and two (2.6%) ID-TLRs by PCI in the paclitaxel arm. The total hierarchical MACE rate was 2.7% (6/222) in the everolimus-eluting arm vs. 6.5% (5/77) in the paclitaxel-eluting arm. In addition there were two (0.9%) ID-TVRs (non-target lesions) in the everolimus arm and none in the paclitaxel arm. There were 0.9% (2/222) and 2.6% (2/77) non-ID TLRs in the two arms respectively.

There were no occurrences of acute or sub-acute stent thromboses in either arm. One case of late stent thrombosis occurred in the everolimus arm at 53 days following a complex procedure with multiple stent implants. One case of late stent thrombosis occurred also in the paclitaxel arm at 56 days post procedure. The latter patient presented with a myocardial infarction and subsequently died. Both patients were taking dual antiplatelet therapy at the time of their thrombotic event.

Discussion

The Spirit II trial has met its primary endpoint, namely it shows an in-stent late loss in the everolimus arm, which is not only non-inferior but also superior to the in-stent late loss observed in the paclitaxel arm.

At the time of the design of the trial, it was decided – in order to avoid potential inter-lesion dependence[20] – to analyse only one lesion per patient (selected by a randomised process) for the primary endpoint, when the patient had received a stent in two different target vessel lesions (17% in the XIENCE V arm and 18% in the TAXUS arm). When all lesions were included in the analysis, the in-stent late loss remained unchanged (0.11 mm vs. 0.12 mm in the XIENCE V arm and 0.36 mm vs. 0.37 mm in the TAXUS arm). (Table 2).

Although a 3:1 randomisation everolimus vs. paclitaxel was performed, which provided more precision for the everolimus arm, without loss of power for the comparison; this might have resulted in a small imbalance in baseline characteristics pre- and post-procedure.

A trend towards a smaller pre-procedural vessel size in the everolimus arm was observed and this difference became significant post-procedure. These differences in vessel size and MLD post-procedure between the two arms could have impacted the restenosis rate and late loss as frequently demonstrated in the literature.[21-23] The MLD post-procedure in the everolimus arm is significantly smaller than the MLD post-procedure in the paclitaxel arm; this is the result of a smaller pre-treatment MLD (p-value 0.032) combined with a smaller acute gain (ns), although the deployment was done at equal levels of pressure. Despite this potential handicap at baseline, in-stent LL and%DS at follow up were significantly lower in the everolimus arm. This small difference in vessel size at baseline is also exemplified in stent volumes measured at baseline (162 mm^3 vs. 195 mm^3) and at follow-up (167 mm^3 vs. 192 mm^3) between the everolimus and paclitaxel arms respectively. Although this difference in stent volume does not achieve significance, it could have also impacted the late proliferative process as previously reported in the literature.[24] Nevertheless, we found a profound and highly significant reduction (73% reduction) in neointimal volume in the everolimus arm (3.8 mm^3) when compared to the paclitaxel arm (14.4 mm^3). Of interest was that in the IVUS findings of the SIRIUS study, assessing the efficacy of a DES coated with a comparable limus, an almost equal neointimal volume of 4.1 mm^3 was found.

Whether malapposition can be held responsible for late stent thrombosis in patients who receive drug-eluting stent remains so far unknown.[25,26] In the present population both drug-eluting stents show negative values of late loss, but the frequency of observations of negative late loss values within the everolimus arm is higher than in the paclitaxel arm (71/237=30% vs. 14/86=16%). The largest negative value was observed in the everolimus arm (–0.57 mm compared to –0.37 mm) in the paclitaxel arm. However, we must recognise that late loss is a parameter with a rather large standard deviation when inter-observer variability is assessed (1 SD 0.36 mm, 2 SD 0.72)[11]; and that late loss is the result of two individual measurements (MLD post-procedure, and MLD at follow-up) which both have their own inter-observer variability due mainly to the process of calibration.[27] Therefore, a negative late loss of –0.57 mm is still within the limits of the confidence level for the reproducibility of the late loss parameter. To investigate the relationship between late loss and malapposition, we have examined the lesions (n=23) with negative late loss, which were assessed by IVUS at follow-up and which received an everolimus-eluting stent and which could therefore potentially have a late-acquired or persisting stent malapposition. Among the 23 lesions with a negative late loss, there was not a single case of late-acquired malapposition, and only one case of persisting malapposition.

In the present study, the incidence of diabetics in the everolimus- and paclitaxel arms was 23% (51/223) and 24% (18/76) respectively. The in-stent LL in the paclitaxel arm for the diabetic patients was 0.39 mm, which is comparable to the previously reported late loss of 0.43 mm in a meta-analysis of the diabetic subsets of the TAXUS family trials.[28] In contrast, the LL in the diabetic patients in the everolimus arm was only 0.15 mm (SD 0.26) and thereby significantly superior to the loss of the paclitaxel arm which was 0.39 mm (SD 0.34). The difference in in-stent LL between everolimus- and paclitaxel-eluting stent was 0.24 mm (95% confidence interval: –0.41 mm; –0.08 mm). It is noteworthy that this difference is identical to the difference in late loss observed in the whole population, and thus indicates also superiority of everolimus-eluting stent versus the paclitaxel eluting stent in terms of LL reduction in the diabetic subset. However as this was not a pre-planned analysis further studies will be required to confirm this.

Conclusions

This non-inferiority randomised trial not only met its primary endpoint, but also demonstrated the superiority of the everolimus-eluting XIENCE V stent over the TAXUS paclitaxel-eluting stent in terms of in-stent late loss. In addition, the IVUS results showed that the XIENCE V stent was more effective at reducing neointimal hyperplasia than the TAXUS stent. The incidence of major adverse events was low and comparable between both treatment arms.

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Appendix I

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A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after successful coronary balloon angioplasty

Final results of the fluvastatin angiographic restenosis (FLARE) trial

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Background The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors competitively inhibit biosynthesis of mevalonate, a precursor of non-sterol compounds involved in cell proliferation. Experimental evidence suggests that fluvastatin may, independent of any lipid lowering action, exert a greater direct inhibitory effect on proliferating vascular myocytes than other statins. The FLARE (Fluvastatin Angioplasty Restenosis) Trial was conceived to evaluate the ability of fluvastatin 40 mg twice daily to reduce restenosis after successful coronary balloon angioplasty (PTCA).

Methods Patients were randomized to either placebo or fluvastatin 40 mg twice daily beginning 2–4 weeks prior to planned PTCA and continuing after a successful PTCA (without the use of a stent), to follow-up angiography at 26 ± 2 weeks. Clinical follow-up was completed at 40 weeks. The primary end-point was angiographic restenosis, measured by quantitative coronary angiography at a core laboratory, as the loss in minimal luminal diameter during follow-up. Clinical end-points were death, myocardial infarction, coronary artery bypass graft surgery or re-intervetion, up to 40 weeks after PTCA.

Results Of 1054 patients randomized, 526 were allocated to fluvastatin and 528 to placebo. Among these, 409 in the fluvastatin group and 427 in the placebo group were included in the intention-to-treat analysis, having undergone a successful PTCA after a minimum of 2 weeks of pre-treatment. At the time of PTCA, fluvastatin had reduced LDL cholesterol by 37% and this was maintained at 33% at 26 weeks. There was no difference in the primary end-point between the treatment groups (fluvastatin $0{\cdot}23 \pm 0{\cdot}49$ mm vs placebo $0{\cdot}23 \pm 0{\cdot}52$ mm, $P=0{\cdot}95$) or in the angiographic restenosis rate (fluvastatin 28%, placebo 31%, chi-square $P=0{\cdot}42$), or in the incidence of the composite clinical end-point at 40 weeks (22·4% vs 23·3%; logrank $P=0{\cdot}74$). However, a significantly lower incidence of total death and myocardial infarction was observed in six patients (1·4%) in the fluvastatin group and 17 (4·0%) in the placebo group (log rank $P=0{\cdot}025$).

Conclusion Treatment with fluvastatin 80 mg daily did not affect the process of restenosis and is therefore not indicated for this purpose. However, the observed reduction in mortality and myocardial infarction 40 weeks after PTCA in the fluvastatin treated group has not been previously reported with statin therapy. Accordingly, a priori investigation of this finding is indicated and a new clinical trial with this intention is already underway.
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Introduction

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (statins) are the most recently introduced class of agents aimed at the management of hyperlipidaemia. Many clinical studies have suggested that their beneficial effect on the progression of atherosclerosis is due to their lipid lowering properties[1,2], although there is growing evidence that they may have additional effects beyond LDL cholesterol reduction[3]. For example, in vitro studies have suggested that, by inhibiting mevalonate synthesis, they may limit the availability of isoprene units and as a consequence, retard such fundamental biological processes as cell growth and proliferation[4].

A direct effect of four statins (simvastatin, lovastatin, pravastatin and fluvastatin) on smooth muscle cell proliferation, independent of any lipid lowering action was demonstrated in an experimental investigation in normocholesterolemic rabbits[5]. Fluvastatin appeared to inhibit neointimal formation to the greatest extent and thus provided a rationale for investigation of the potential effect of fluvastatin for the prevention of restenosis after coronary balloon angioplasty in a large clinical trial. Accordingly, the FLARE—Fluvastatin Angioplasty Restenosis trial was designed.

Methods

Protocol development for this randomized double-blind placebo-controlled trial commenced as long ago as early 1992, in collaboration with a nucleus of committed expert physicians who subsequently formed the trial steering committee: the Cardialysis Clinical Trial Co-ordinating Centre, Rotterdam, Netherlands and Sandoz Pharma, AG, Basel (now Novartis Pharma, AG., the trial sponsors and proprietors of fluvastatin/lescol). To facilitate the successful performance of the trial, especially with regard to standardized performance of coronary angiography (suitable for optimal quantitative analysis at the core laboratory) by the 33 investigating centres, throughout seven European countries, extensive preparatory and background work was required. This included several national and international general investigators meetings to describe the protocol and trial documentation, visits by quantitative coronary angiography experts from the co-ordinating centre and representatives of the Sandoz Affiliated Companies to all centres, and the performance of angiographic test cases by investigators (with critical evaluation by the core laboratory), to demonstrate their suitability to participate in the trial. A number of prospective investigating centres, which were routinely recording angiograms on videotape instead of on cinefilm, had to be excluded from the trial after reproducibility testing at the core laboratory demonstrated unreliability of video as a substrate for image storage for subsequence quantitative coronary angiography analysis[7].

Inclusion/exclusion

Patients to be included in the trial were those with symptomatic or ischaemia-producing coronary lesions suitable for balloon angioplasty, according to the local practice of the investigator, and an LDL cholesterol $<6{\cdot}0$ mmol . l^{-1}. Initially, only patients requiring angioplasty of a single target lesion were to be included, but because of investigator opinion, that evolving clinical practice indicated an increasing proportion of multi-lesion procedures, the protocol was amended in January 1994 to allow planned multilesion angioplasty. Principal trial exclusion criteria were myocardial infarction within the previous 3 months (making measurement of some serum lipid fractions unreliable), restenotic lesions, lesion in a bypass graft, patients requiring urgent angioplasty or inability to defer angioplasty for 2 weeks in order to allow pre-treatment, and a fasting low-density lipoprotein cholesterol >6 mmol . l^{-1} or triglycerides $>4{\cdot}5$ mmol . l^{-1} at screening.

Intention-to-treat population and sample size calculation

The trial commenced with inclusion of the first patient in October 1993. By July 1995 the recruitment target of 1000 patients had been exceeded, with a total of 1054 patients randomized to receive either fluvastatin 40 mg (n=526) or placebo (n=528), twice daily. This patient group formed the total population for evaluation of the safety of the trial medication. This was independently evaluated by a Safety and Data Monitoring Committee, formed by internationally recognized expert epidemiologists and cardiologists, not involved with patient treatment in the trial. The protocol was carefully designed primarily to investigate the influence of fluvastatin on restenosis after successful angioplasty. The intention-to-treat population was defined as 'those randomized patients who had taken at least one tablet of trial medication and undergone successful balloon angioplasty' (without the use of a stent) 2 ± 2 weeks later. At the time the protocol was finalized (mid 1993), limited data existed on the intermediate (6 month–1 year) results of stent implantation. The indications were uncertain and use varied widely throughout the participating countries. Accordingly, it was decided by the steering committee that all patients undergoing stent implantation during the initial angioplasty procedure would be considered to have had an unsuccessful balloon angioplasty and would be excluded from the intention-to-treat population. It seemed at that time that the incidence of so-called 'bail-out stent implantation' was generally less than 10% and this was taken into account in the estimation of patient inclusion required to test the trial hypothesis with 90% statistical certainty.

The calculation of sample size was based on the knowledge that the mean luminal loss during follow-up after successful PTCA among placebo-treated groups in

Table 1 Flow chart of all patients randomized (n=1054)

	Number of patients	
	Fluvastatin	Placebo
Safety population	526	528
Medication discontinued before PTCA	10	6
Consent withdrawn before PTCA	7	6
Delayed exclusion	10	9
PTCA cancelled	13	7
MACE before PTCA	4	3
MACE during PTCA	72	71
Protocol violation	1	1
Intention-to-treat population	409	425
Angiographic population	382	391

MACE=major cardiac events.

four previous trials with different agents was 0·30 mm[8–10]. Thus it was assumed that the placebo group in the FLARE trial would demonstrate a similar degree of loss. The target treatment effect was decided upon by the steering committee as a 40% reduction in luminal loss by fluvastatin. In order to detect such a difference, with 90% power at an alpha level of 0·05, approximately 730 evaluable patients were required. Allowing for an estimated 'drop out' rate of 15% (based on experience with previous trials and taking account of the pre-treatment phase required in the FLARE trial), a total of 850 patients needed to be randomized. This number of evaluable patients also allowed the detection of a difference of 30% in the incidence of major adverse cardiac events (death, myocardial infarction, coronary artery bypass graft survey or re-intervention) between the treated and placebo groups, with a power of >90% at an alpha level of 0·05. However, as a consequence of evolving angioplasty practice, principally the increasing use of coronary stents, a 22% 'drop out' rate was observed in the early months of the trial. The steering committee therefore took the decision to increase the recruitment target to 1000 patients to ensure that an adequate number of evaluable patients would be enrolled. Ultimately, 834 evaluable patients, 409 patients in the fluvastatin group and 425 in the placebo group, had a successful balloon and continued on trial medication until follow-up angiography at 26 ± 2 weeks after angioplasty (flow chart is shown in Table 1).

Trial chronology

The trial commenced (visit 1, 2–4 weeks before intervention) when eligible patients who had been screened and fulfilled all inclusion criteria[12] and had given informed consent were randomized. After a minimum of 2 weeks, the patient returned for PTCA, prior to which clinical and laboratory assessments were carried out (visit 2, week 0). Patients undergoing successful PTCA (defined as diameter stenosis <50%) without reaching a major adverse cardiac event, continued on trial medication. A clinical follow-up visit, with clinical evaluation and lipid and biochemical assessment was required 6 weeks after PTCA (visit 3, week 6) and a further visit with exercise testing (visit 4, 24 ± 2 weeks after angioplasty), was required prior to follow-up angiography, which was carried out 26 ± 2 weeks after PTCA (visit 5). In order to allow sufficient time for performance of justified (on the basis of recurrent symptoms or demonstrated exercised-induced ischaemia) elective re-intervention or bypass graft surgery arising from clinical and angiographic follow-up at 26 ± 2 weeks, the final clinical follow-up for evaluation of clinical end-points was at 40 weeks after PTCA (visit 6, week 40). Due to variable waiting times for elective surgical or non-surgical intervention throughout the participating countries, 40 weeks was agreed upon as the most practical timing for final clinical follow-up.

End-points

Primary end-point

The primary end-point for the FLARE trial was the absolute change in minimal luminal diameter, between the post-PTCA and follow-up angiogram, 26 ± 2 weeks later, measured by quantitative coronary angiography. If, for whatever reason, angiography was carried out prior to 14 weeks after PTCA, further angiography within the recommended time-window was required, unless a clinical end-point, as defined below, had been reached.

Secondary angiographic end-points

(i) Minimal luminal diameter at follow up angiography; (ii) incidence of restenosis, as defined according to categorical angiographic criteria.

Clinical end-points

A clinical end-point was considered to have been reached upon the occurrence of any one of the major cardiac events described below, before 40 weeks post-PTCA, whereby for any patient experiencing more than one event, the first event reached was considered:

1. death—post-mortem examination was recommended in all patients randomized who died during the course of the trial. In the absence of clear evidence to the contrary, any deaths occurring during the trial were considered to be cardiac;
2. non-fatal myocardial infarction. The occurrence of myocardial infarction was defined as the finding of a typical temporal pattern of serum cardiac enzyme change, in particular, documented elevation of serum creatine phosphokinase levels to greater than twice the upper limit of normal for the laboratory and/or a greater than twofold increase in the creatine phosphokinase MB fraction, with return to within the accepted normal range. In the absence of unambiguous cardiac enzyme abnormalities, the finding of typical evolutional ECG patterns of myocardial infarction, or of 'new' pathological Q waves were considered diagnostic of myocardial

infarction. Evidence to support the diagnosis of myocardial infarction had to be provided by the investigator, to facilitate final adjudication by the Critical Events and Safety and Data Monitoring Committees;
3. coronary artery bypass graft surgery (CABG);
4. re-intervention after completion of the initial PTCA procedure and before the end of the trial period, including requirement for repeat PTCA or intervention using an alternative percutaneous revascularization device (use of a perfusion balloon catheter at the discretion of the treating physician was acceptable and did not constitute an end-point or exclusion from the trial). Stent implantation during the index angioplasty procedure was considered to indicate unsuccessful balloon angioplasty and the patient was excluded from the intention-to-treat analysis.

Lipid and laboratory aspects
Patients with a measured fasting LDL cholesterol above 6·0 mmol . l^{-1} or fasting triglyceride level greater than 4·5 mmol . l^{-1} (by local laboratory) within 4 weeks of randomization were excluded from the trial, on the ethical principle that they required lipid-lowering therapy. The effect of trial medication on serum lipids was assessed by performing a comprehensive lipid profile (total cholesterol, low and high density lipoprotein cholesterol, lipoprotein (a), apolipoprotein A1 and B and triglycerides) at all clinical visits[13]. Lipid parameters and temporal changes were compared between the two groups and correlated with the angiographic and clinical end-points. In addition, prior to randomization, all patients had to have documented haematological, hepatic and renal indices and creatine phosphokinase levels within the reference range for the analysing laboratory. At randomization, blood samples were taken for measurement of these parameters at a central laboratory. Similar laboratory tests were repeated at each attendance, to detect any potential adverse biochemical or haematological effects of trial medication. In the final analysis, the treatment and placebo groups were compared for frequency and severity of abnormalities detected. From randomization, all blood samples were specially packaged in protective containers and sent by courier to central laboratories for blinded analysis. Local laboratory results were used for screening and establishment of patient suitability for inclusion, as well as for diagnosis of acute adverse events (all data pertaining to such events were evaluated blindly by the Critical Events Committee and by the Safety and Data monitoring Committee). Central laboratory results were used to monitor the safety of trial medication and relevant laboratory abnormalities were reported to responsible investigators and to the Clinical Co-ordinating Centre.

Trial medication

Compliance, safety and tolerability
In addition to laboratory tests, compliance with trial medication was assessed at each visit and all adverse experiences (any deterioration in clinical status during the course of the trial was considered an adverse experience; its relationship with trial medication was determined according to well known guidelines) were documented in the case record form. The trial medication was discontinued if: (1) the PTCA procedure was not performed for whatever reason; (2) the PTCA procedure was unsuccessful (failure to achieve a % diameter stenosis <50% post PTCA, without the use of a device other than balloon) whether or not a major cardiac event occurred; (3) a primary clinical end-point was reached, or another serious adverse event occurred; (4) a protocol violation occurred. Discontinuation of trial medication after successful angioplasty did not dictate withdrawal from the trial, and follow-up clinical observations had to be made as scheduled, to complete the evaluation and analysis.

Concomitant medication

All patients received acetyl salicylic acid up to 325 mg once daily throughout the trial period. Intracoronary injection of 1–3 mg isosorbide dinitrate or 0·1–0·3 mg glyceryl trinitrate, was systematically used to control vasomotor tone. Oral or sublingual nitrates could be given during the follow-up period where indicated. At the discretion of the treating physician, during the PTCA procedure or the in-hospital period, beta-blockers and calcium antagonists could be prescribed. Non-aspirin antiplatelet agents and oral anticoagulants were discouraged.

Excluded medications, which were considered to potentially interfere with evaluation or interpretation of study results, included: all other lipid lower agents; steroid hormones or oral contraceptive agents; thyroid hormone replacement, if not stable for at least 2 months prior to the study or likely to change during the study; erythromycin or ketoconazole; cyclosporin; anti-epileptic therapy; and, at the beginning of the trial, oral hypoglycaemic agents (this exclusion was cancelled within 3 months of the beginning of the trial, based on data from the manufacturing company).

Statistical analysis

Continuous variables, including in particular the change in minimal luminal diameter during follow-up and the minimal luminal diameter at follow-up, were compared by analysis of variance techniques, taking potential centre (investigating institution) interaction into account. Categorical variables were compared by Mantel–Haenszel test procedures. Major cardiac events were displayed using the Kaplan–Meier method; statistical comparisons were performed using the logrank test. Binary restenosis rates (according to the conventional definitions employed) were compared by Fisher's exact test.

Angioplasty procedure and angiographic protocol to facilitate quantitative analysis

The angioplasty technique was left to the discretion of the treating physician, except for the performance of coronary angiography before and after successful lesion treatment. To this end, all investigators were required to receive instruction from the core laboratory (Cardialysis, Rotterdam, the Netherlands) in the appropriate recording of angiograms to facilitate quantitative analysis. Two angiographic 'test runs' had to be submitted to the core lab for evaluation and approval before a centre could begin to recruit patients. Angiograms had to be recorded on cinefilm at a frame speed of 25 mm . s^{-1}; recordings pre-PTCA and the final post-PTCA recording had to be made after intracoronary injection of nitroglycerin or isosorbide dinitrate, beginning with the empty contrast catheter tip. Contrast opacification had to be optimal and in at least two projections (separated by at least 30° angulation) clearly showing the target lesion and adjoining segments proximal and distal. All film sequences, medications and materials used (including details of balloon inflations), a qualitative angiographic evaluation of the lesion morphology, angiographic outcome, and complications were recorded on a dedicated case record form (called the Technician's Worksheet). All further angiographic procedures, including intercurrent and follow-up angiograms and repeat angioplasty, had to be similarly documented in detail; angiographic film sequences had to be repeated in projections identical to those used during the index procedure.

Core laboratory angiographic evaluation procedures

All cineangiograms were evaluated by teams of two experienced observers for detailed qualitative features. The inter and intra-observer variability for evaluation of these features for this core laboratory had been previously published[14]. Quantitative angiographic measurements were performed using the Cardiovascular Angiographic Analysis System (CAAS) using standardized methodology which has been extensively described[15].

Results

Patients

Of the 1054 randomized patients, 34 in the fluvastatin group and 22 in the placebo group did not complete the pre-treatment period and undergo angioplasty (because of withdrawal of consent, discontinuation of trial medication, experience of a major adverse cardiac event or cancellation of angioplasty—Table 1). A further 83 patients in the fluvastatin group and 81 in the placebo group underwent an angioplasty procedure, but had an unsuccessful or complicated outcome (including death n=2; myocardial infarction n=10; emergency coronary artery bypass graft surgery n=7; or necessity for bail-out stent implantation n=67) or had a previously unnoticed exclusion criterion and were later excluded from analysis. Ultimately, a total of 409 patients in the fluvastatin group and 425 in the placebo group had successful balloon angioplasty without adverse cardiac events and entered the intention-to-treat analysis.

Baseline clinical (Table 2) and angiographic characteristics (Table 3) were similarly distributed in the two groups. Patients (83% male) had predominantly single-vessel disease and underwent mainly single-lesion dilatation (85%). The majority of patients (71%) had stable class 0–2 anginal symptoms, although 40% gave a history of recent non-exertional angina. Lesions were located in the left anterior descending artery in a total of 42% of patients, in the right coronary artery in 27% and in the circumflex in 31%. Lesion type was mainly scored as ACC/AHA type B1 or B2 and a TIMI grade 0 or 1 occlusion was encountered in 7%. Additional features of interest include: lesion length was scored as <10 mm in 68% of the fluvastatin group and in 69% of the placebo group, as 10–20 mm in 23% of each group, as longer than 20 mm in 4% and 3%, and as not measurable in 5%. Calcification was scored in 18% of target lesions and thrombus in 1·8%, lesions were located in a tortuous segment in 16% of lesions in each group. A branch point was present in the stenosis, or was covered by the dilating balloon, in 45% of patients in the fluvastatin group and in 47% in the placebo group.

Lipid levels and other laboratory parameters (Tables 2 and 4)

Baseline lipid parameters were similar in the two groups. At the angioplasty visit (week zero, 2 weeks after commencing trial medication), LDL cholesterol was reduced by 37% in the fluvastatin group and maintained at 33% at the 26 week follow-up, whereas in the placebo group no significant change in LDL cholesterol was observed. In addition, at 26 weeks a 28% reduction in apolipoprotein B was observed, as well as a 13% reduction in triglycerides, in contrast to no significant change in the placebo group. No significant changes were observed in HDL cholesterol, apolipoprotein A1 or lipoprotein (a). A more than three-fold elevation above reference was observed in serum ALAT in 1·7% of patients in the fluvastatin group and in 0·7% in the placebo group, and in ASAT in 0·5% in each group. However, no patient showed such abnormalities in two consecutive samples. Elevation of total creatine phosphokinase to more than 10 times the upper range (the level required to define myopathy[16]) was not observed.

Table 2 Baseline demographic characteristics of the intention-to-treat population (n=834)

	Fluvastatin (409 patients)		Placebo (425 patients	
Age	60 ± 9		61 ± 9	
Male	339	83%	349	82%
Relevant medical history				
Diabetes mellitus	15	4%	19	5%
Prior MI	134	33%	141	33%
Prior CABG	18	4%	21	5%
Prior PTCA	38	9%	38	9%
Cerebrovascular disease	14	3%	15	4%
Hypertension	136	33%	140	33%
Peripheral vascular disease	35	9%	36	9%
Current smoking	125	31%	116	27%
Family history of coronary disease	134	33%	135	32%
Lipid profile				
Total cholesterol (mmol . l^{-1})	5·75 ± 1·01		5·77 ± 1·03	
LDL cholesterol (mmol . l^{-1})	3·96 ± 0·85		3·95 ± 0·87	
HDL (mmol . l^{-1})	1·06 ± 0·27		1·08 ± 0·28	
Triglycerides (mmol . l^{-1})	1·69 ± 0·84		1·6 ± 0·83	
Lipoprotein-a (mg . dl^{-1})	29·5 ± 40·0		32·2 ± 44·1	
Anginal status				
No angina	49	12%	45	11%
CCS class 1	57	14%	58	13%
CCS class 2	179	44%	207	49%
CCS class 3	111	27%	103	24%
CCS class 4	13	3%	12	3%
Recent history of non-exertional angina	163	40%	177	42%
Body mass index	26·7 ± 3·3		26·7 ± 3·2	
Extent of coronary artery disease				
Unknown	11	3%	2	?1%
Single vessel disease	276	67%	316	74%
Two vessel disease	93	23%	88	21%
Triple vessel disease	29	7%	19	4%
Number of lesions	479		495	
Patients with multilesion PTCA	63	15%	59	14%

CCS=Canadian Cardiovascular Society.

Table 3 Baseline lesion characteristics of the intention-to-treat population (n=834)

	Fluvastatin (479 lesions)		Placebo (495 lesions)	
Lesion type (ACC/AHA)				
A	33	7%	40	8%
B1	202	42%	195	39%
B2	221	46%	242	49%
C	21	4%	18	4%
Missing	16	3%	18	4%
Lesion location				
Left anterior descending	210	44%	191	39%
Right coronary artery	128	7%	137	27%
Circumflex	141	29%	161	34%
TIMI flow status pre-PTCA				
TIMI 0	21	4%	22	4%
TIMI 1	14	3%	26	5%
TIMI 2	60	13%	48	10%
TIMI 3	383	80%	399	81%
Missing	1	0%	0	0%

ACC/AHA=American College of Cardiology/American Heart Association; TIMI=Thrombolysis in Myocardial Infarction.

Angiographic outcome (Table 5 and Fig. 1)

In the intention-to-treat population 773 patients (93% of those eligible) completed angiographic follow-up suitable for quantitative analysis. Target vessel size was 2·66 mm in each group. Minimal luminal diameter pre-angioplasty was 0·97 mm in the fluvastatin group and 0·96 mm in the placebo group, increasing to 1·78 mm in the fluvastatin group and 1·77 mm in the placebo group, giving an acute luminal gain of 0·81 mm and 0·80 mm, respectively. The frequency of angiographic dissection scored by the angiographic core laboratory was 44% in the fluvastatin and 47% in the placebo group. Late luminal loss was identical in both groups (0·23 mm) and follow-up minimal luminal diameter was similar at 1·55 mm in the fluvastatin group and 1·53 mm in the placebo group, reflected by superimposition of the cumulative frequency distribution curves in Fig. 1. The categorical restenosis rate (diameter stenosis >50%) was 28% in the fluvastatin group and 31% in the placebo group (P=0·42).

***Table 4** LDL cholesterol volumes of intention-to-treat population during treatment period*

	Fluvastatin (409 patients)	Placebo (425 patients)	Difference	
Week −2 (baseline)	3·96 ± 0·85	3·95 ± 0·87	0·01	P=1·00
Week 0 (procedure)	2·46 ± 0·74	3·81 ± 0·79	0·35	P<0·0001*
Week 4	2·56 ± 0·71	3·88 ± 0·85	0·32	P<0·0001*
Week 26	2·63 ± 0·78	3·85 ± 0·84	0·22	P<0·0001*

*P value adjusted for baseline value.

***Table 5** Results of per lesion based offline Quantitative Coronary Angiographic analysis before and after angioplasty and at 6 month follow up in patients with evaluable angiograms (n=773)*

	Fluvastatin (445 lesions in 382 patients)	Placebo (458 lesions in 391 patients)	P value for difference
Reference vessel diameter (mm)			
Pre-PTCA	2·66 ± 0·50	2·66 ± 0·54	P=0·99
Post-PTCA	2·75 ± 0·48	2·72 ± 0·51	P=0·56
Follow-up	2·79 ± 0·54	2·76 ± 0·60	P=0·79
Minimal luminal diameter (mm)			
Pre-PTCA	0·97 ± 0·41	0·96 ± 0·41	P=0·67
Post-PTCA	1·78 ± 0·36	1·77 ± 0·36	P=0·57
Follow-up	1·55 ± 0·59	1·53 ± 0·58	P=0·77
Percent diameter stenosis			
Pre-PTCA	63 ± 14%	63 ± 15%	P=0·79
Post-PTCA	35 ± 8%	35 ± 8%	P=0·72
Follow-up (mm)	44 ± 18%	44 ± 17%	P=0·96
Acute luminal gain (mm)	0·81 ± 0·42	0·80 ± 0·43	P=0·93
Late luminal loss (mm)	0·23 ± 0·49	0·23 ± 0·52	P=0·95
Net luminal gain (mm)	0·57 ± 0·55	0·57 ± 0·57	P=1·00
Restenosis rate (% diameter stenosis at follow up ≥50%)	126 28%	141 31%	P=0·42

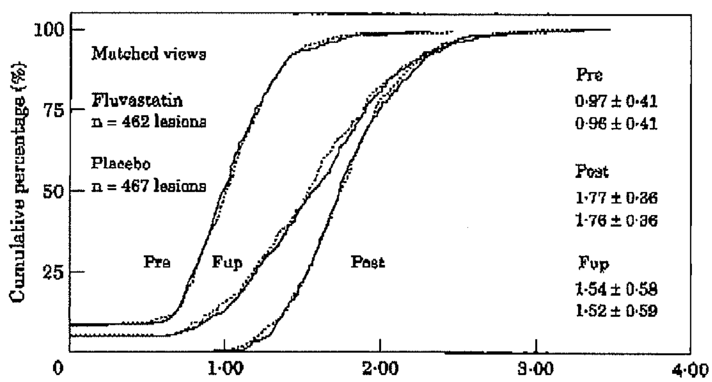

Figure 1 **Cumulative frequency distribution curves for all evaluable lesions in the two treatment groups, showing minimal luminal diameter before (Pre) and after (Post) intervention and at follow-up (Fup).**

Clinical results (Table 6 and Fig. 2(a) and (b))

Major cardiac events were observed in 92 patients in the fluvastatin group and in 99 in the placebo group (P=0·74). Death or myocardial infarction occurred in 1·4% of patients in the fluvastatin group compared with 4% of patients in the placebo group (P=0·03) and re-intervention (surgical or percutaneous) was carried out in 21% of the fluvastatin-treated patients and 19·3% of the placebo patients. At 26 weeks, prior to follow-up angiography, 69% of patients in the fluvastatin group and 70% in the placebo group were angina free.

***Table 6** Major adverse cardiac events occurring during follow-up, assessed at 40 weeks after angioplasty in the intention-to-treat population (n=834)*

	Fluvastatin (409 patients)		Placebo (425 patients)			Fluvastatin (409 patients)		Placebo (425 patients)		Difference	
Worst event					Cumulative events						
Death	3	0·7%	7	1·6%	Death	3	0·7%	7	1·6%		$P=0.37$
MI	3	0·7%	10	2·4%	Death/MI	6	1·4%	17	4·0%		$P=0.03$
CABG	18	4·4%	10	2·4%	Death/MI/CABG	24	5·8%	27	6·4%		$P=0.88$
rePTCA	68	16·6%	72	16·9%	Death/MI/CABG/rePTCA	92	22·4%	99	23·3%		$P=0.85$

MI=myocardial infarction; CABG=coronary artery bypass grafting; rePTCA=percutaneous transluminal coronary angioplasty reintervention.

Non-cardiac adverse events

A total of four patients (0·8%) in the fluvastatin group and 11 (2·1%) in the placebo group were diagnosed with malignant disease during the trial period. In 45% of patients in the fluvastatin group and 51% in the placebo group a minor adverse event was reported. Principal among these events, where more than a 1% difference existed between the two groups (fluvastatin vs placebo), were: headache (3·8% vs 1·7%), nausea (3·4% vs 2·3%), myalgia (1·7% vs 0·6%) or other pain (4·4% vs 2·5%); however, none of these differences was statistically significant.

Discussion

Design

The primary goal of this randomized placebo-controlled trial was to evaluate the effect of high dose fluvastatin (80 mg daily), with a pre-treatment period of 2–4 weeks and a duration of 26 weeks, on restenosis after successful balloon angioplasty, as measured by quantitative angiography. Accordingly, the study was powered to detect a 40% reduction in quantitative coronary angiography measured luminal loss, from an expected 0·30 mm in the placebo group to 0·18 mm in the fluvastatin group. Of the total recruitment of 1054 patients, 834 underwent a successful balloon angioplasty after receiving at least one dose of trial medication, thus forming a more than adequate intention-to-treat population. Angiographic follow-up of 93% provided a more than ample patient population to test the trial hypothesis.

The loss in minimal luminal diameter from post-angioplasty to follow-up angiography was used as a surrogate for intimal hyperplasia, since we were investigating the anti-proliferative effect of fluvastatin. Of course other angiographic measurements[12] were also included as secondary and tertiary end-points and ultimately no differences were detected between the fluvastatin and placebo group so the outcome of the trial was negative.

It is noteworthy that the mean loss observed in this trial is the lowest ever published in a balloon angioplasty population — 0·23 mm in both groups, compared with an average of 0·30 mm in the CARPORT, MERCATOR, MARCATOR and PARK trials[17], all co-ordinated by this core laboratory. In two other restenosis trials using statins, the reported luminal loss was also greater, at 0·46 mm in the lovastatin trial[18] and in the PREDICT (pravastatin)[19] trial, although the minimal luminal diameter at follow-up is in the same range in all three studies (1·45 mm in lovastatin, 1·51 mm in PREDICT and 1·54 mm in FLARE) and the rate of revascularization during follow-up is consistent in all three trials (in the range of 21%). Differences in the patient populations may be responsible for the greater loss in the lovastatin trial compared with FLARE. In the lovastatin trials, the patient population included 55% CCS class 3 or 4 angina, compared to 30% in FLARE; diabetics formed 12% of the population in lovastatin and 4·5% in FLARE; females made up 29% of the lovastatin trial population compared with 19% in FLARE; 44% of patients in the lovastatin trials had multivessel disease compared with 33% in FLARE; 26% of patients had multilesion dilatation in lovastatin and 15% in FLARE; also, the intention-to-treat population in FLARE excluded the patients with stent implantation, which is known to be associated with greater luminal loss during follow-up than balloon angioplasty, despite the more favourable late outcome[20]. Lastly differences in quantitative coronary angiography methodology may play a part, as has been previously published by our group[21].

Effects of fluvastatin in FLARE

Why did fluvastatin not diminish restenosis?

For the first time, a pharmacological agent with proven ability to inhibit human smooth muscle cell proliferation in vitro has been tested in a clinical trial. In-vitro investigation of the pharmacological activity of sera from patients treated with either pravastatin or fluvastatin on proliferation of cultured human smooth muscle cells and on cholesterol biosynthesis, showed similar effects on plasma lipids and lipoproteins, but in addition, fluvastatin sera caused significant inhibition of smooth muscle cells proliferation (−28% cell growth),

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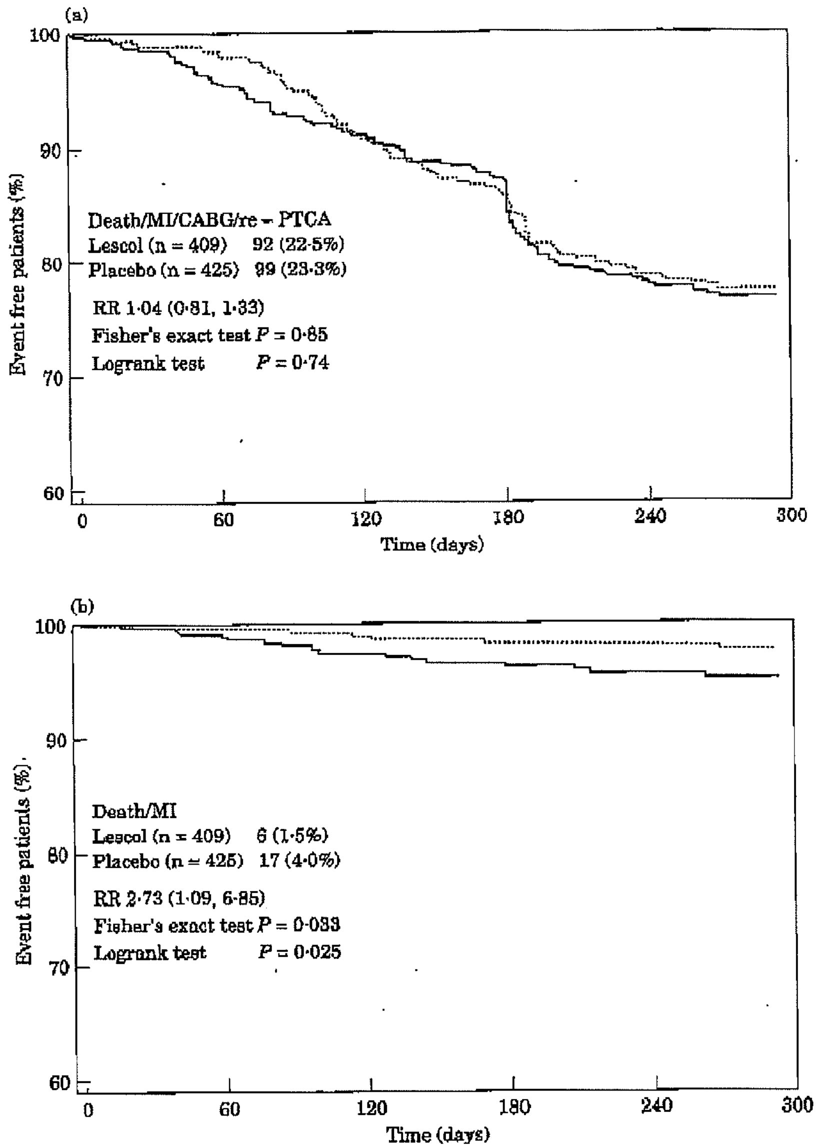

Figure 2 **(a) Event-free survival curves with respect to all major cardiac events for both treatment groups. *P* values are calculated using the logrank test. (b) Event-free survival curves with respect to the combined end-point death and myocardial infarction (MI) for both treatment groups. *P* values are calculated using the logrank test.**

whereas pravastatin sera exhibited no such effect[26]. This was the first demonstration that a statin might inhibit human myocyte proliferation. Despite the achievement of effective serum levels and adequate pre-treatment to reach appropriate tissue levels, the in-vitro observed efficacy did not translate into in-vivo effect on restenosis, as measured by quantitative coronary angiography. Compliance with study medication was considered satisfactory, as judged by the LDL cholesterol changes already observed at the angioplasty visit (2 weeks after initiating therapy) and maintained at follow-up angiography. To attempt to explain the apparent lack of effect, a number of scenarios may be considered. Firstly, although the experimental evidence indicates that the action of fluvastatin is observed in all activated cells (due to the inhibition of mevalonate synthetase), it is possible that the smooth muscle cells in culture may not appropriately model the hypertrophic, hyperplastic myocyte changes triggered by angioplasty. Experimental exposure of isolated

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myocytes to fluvastatin in the culture medium may be quite different from the in-vivo situation, especially of proliferation after angioplasty is initiated from deep within the arterial media or adventitia[22].

Secondly, examination of the results observed in the in-vitro human arterial model suggests that the inhibitory effect of fluvastatin in-vitro may be variable. In the clinical situation, which is characterized by fluctuations in the drug plasma level, it is conceivable that a steady state inhibition is not reached. Consequently, at times, growth suppression may be in abeyance, allowing sufficient proliferation to promote restenosis. Moreover, extensive studies of regional intracoronary pharmacokinetics (using radiolabelling) have revealed that even locally administered compounds in apparently effective doses, proportionally much higher than could be given orally, fail to reach adequate pharmacodynamic concentrations at the target site[23].

Thirdly, restenosis is a much more complex process than simple proliferation. Cellular matrix production and the only recently intracoronary ultrasound demonstrated phenomenon of chronic vessel remodelling may explain at least 50% of the luminal loss in the 6 months after successful angioplasty[24]. The implication of this is that since quantitative coronary angiography cannot provide measurements of these components of luminal renarrowing, a potential anti-proliferative effect of fluvastatin might have been masked by a lack of effect on vessel retraction or remodelling. Serial intracoronary ultrasound would be required to detect such subtle potential differences in the vessel wall response to balloon injury between the treatment groups, but when FLARE was conceived, intracoronary ultrasound was still very much investigational and not widely used and the described phenomena had not yet been recognized.

It is thus conceivable that fluvastatin may have had some inhibiting effect on smooth muscle cell proliferation in FLARE without actually affecting luminal loss, although the complete superimposition of the cumulative distribution curves for minimal luminal diameter indicate absence of even the slightest angiographically detectable difference between the treatment and placebo groups. It would be moot to suggest that either matrix production or chronic remodelling could be reasonably expected to be influenced by fluvastatin. Ultimately, the now recognized relative importance of chronic vessel remodelling mitigates against the likelihood of any systemically administered anti-proliferative agent exerting any detectable influence on restenosis after balloon angioplasty. Accordingly, future trials investigating anti-proliferative agents must use a predominantly proliferative clinical model, such as post successful stent implantation, where restenosis really represents new tissue growth[25].

How can the increased infarct free survival in the fluvastatin treated group be explained?

Although this study had a primary angiographic end-point, it was adequately powered to detect a difference in major adverse cardiac events at 40 weeks. At 40 weeks there was no difference in the incidence of the combined clinical end-points of death, myocardial infarction, CABG and re-intervention. However, a significantly lower incidence of death and non-fatal myocardial infarction (1·4% in the fluvastatin group, compared with 4% in the placebo group (P=0·025) relative risk reduction 0·37 [0·18, 0·89]) was observed in the fluvastatin group. This observation, which was not a pre-specified trial end-point in FLARE, was unexpected and has not been described in the lovastatin or PREDICT trials; in fact the frequency of these events was somewhat higher in the lovastatin and pravastatin groups compared to placebo in those trials. However, the finding is in keeping with reduced cardiovascular events observed in angiographic regression trials and the clinical lipid lower trials[26–28]. Accordingly, despite the possibility that this is a chance finding (because of a type II error, reflected by the wide confidence intervals for the relative risk reduction in death or myocardial infarction by fluvastatin), it is possible to explain the finding on the basis of plaque stabilization secondary to effective and rapid reduction in total and LDL cholesterol and apolipoprotein B. There are also potential non-lipid effects of fluvastatin which could explain the observed clinical effect which deserve to be mentioned. Experimental data suggest that fluvastatin can favourably influence thrombogenic and hypofibrinolytic factors involved in acute vascular events. Colli and co-workers[29] have recently demonstrated that fluvastatin, in a dose-dependent manner interferes with macrophage-derived tissue-factor production, while pravastatin had no such effect. The same group showed that fluvastatin can blunt the increased synthesis of endothelium derived PAI-1 induced by oxidized LDL. Additionally fluvastatin 40 mg daily in coronary patients significantly reduces circulating levels of tPa antigen[30], which is considered a marker of endothelial damage. Accordingly, although the clinical benefits in FLARE may have arisen by chance, they do have plausible mechanistic explanations and evaluation in a definitive trial is indicated.

Conclusions

In this adequately powered randomized double-blind placebo-controlled trial, experimentally demonstrated anti-proliferative effects of fluvastatin on human arterial smooth muscle cells failed to translate into a clinical effect in reducing restenosis after successful coronary balloon angioplasty, despite a 2–4 week pre-angioplasty treatment period, whereby adequate tissue levels had been reached. A significantly lower incidence of death and myocardial infarction was, however, observed in the fluvastatin treatment group, representing the first demonstration of a potentially important secondary prevention effect of statin therapy only 6 months after successful angioplasty. Although the FLARE trial was not designed or powered to detect such an effect, and it could be serendipitous, this finding has prompted the

inauguration of a new double-blind randomized trial, now already in the inclusion phase, specifically intended to evaluate the effect of long term fluvastatin therapy on the occurrence of major adverse cardiac events after successful percutaneous coronary intervention.

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Actinomycin-eluting stent for coronary revascularization: A randomized feasibility and safety study: The ACTION trial

Patrick W. Serruys, John A. Ormiston, Georgios Sianos, J. Eduardo Sousa, Eberhard Grube, Peter den Heijer, Pim de Feyter, Pawel Buszman, Albert Schömig, Jean Marco, Lech Polonski, Leif Thuesen, Andreas M. Zeiher, J.H. Nicholas Bett, Maarten J. Suttorp, Helmut D. Glogar, Mark Pitney, Gerard T. Wilkins, Robert Whitbourn, Susan Veldhof, Karine Miquel, Rachel Johnson, Leslie Coleman, Renu Virmani, and ACTION Investigators

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CLINICAL RESEARCH **Clinical Trials**

Actinomycin-Eluting Stent for Coronary Revascularization

A Randomized Feasibility and Safety Study: The ACTION Trial

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OBJECTIVES We sought to demonstrate the safety and performance of the actinomycin D-coated Multilink-Tetra stent (Guidant Corp., Santa Clara, California) in the treatment of patients with single de novo native coronary esions.

BACKGROUND Drug-eluting stents (DES) releasing sirolimus or paclitaxel dramatically reduce restenosis. The anti-proliferative drug, actinomycin D, which is highly effective in reducing neointimal proliferation in preclinical studies, was selected for clinical evaluation.

METHODS The multi-center, single-blind, three-arm ACTinomycin-eluting stent Improves Outcomes by reducing Neointimal hyperplasia (ACTION) trial randomized 360 patients to receive a DES (2.5 or 10 $\mu g/cm^2$ of actinomycin D) or metallic stent (MS). The primary end points were major adverse cardiac events (MACE) at 30 days, diameter stenosis by angiography, tissue effects, and neointimal volume by intravascular ultrasound (IVUS) at six months. When early monitoring revealed an increased rate of repeat revascularization, the protocol was amended to allow for additional follow-up for DES patients. Angiographic control of MS patients was no longer mandatory.

RESULTS The biased selection of DES patients undergoing IVUS follow-up invalidated the interpretation of the IVUS findings. The in-stent late lumen loss and that at the proximal and distal edges were higher in both DES groups than in the MS group and resulted in higher six-month and one-year MACE (34.8% and 43.1% vs. 13.5%), driven exclusively by target vessel revascularization without excess death or myocardial infarction.

CONCLUSIONS The results of the ACTION trial indicate that all anti-proliferative drugs will not uniformly show a drug class effect in the prevention of restenosis. (J Am Coll Cardiol 2004;44: 1363–7) © 2004 by the American College of Cardiology Foundation

Restenosis after stent implantation remains a major limitation of efficacy. Drug-eluting stents (DES) with sirolimus (1) and paclitaxel (2) have significantly reduced restenosis in simple lesions, compared with the metallic stent (MS). Actinomycin D affects the "S" phase of the cell cycle by forming a stable complex with double-stranded deoxyribonucleic acid inhibiting ribonucleic acid synthesis and is a powerful inhibitor of cell proliferation (3). To create the eluting stent, actinomycin was coated onto the stainless-steel Multilink Tetra stent in a polymer. We aimed to test the safety and efficacy of two doses of actinomycin D compared with the MS.

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METHODS

Study design. This was a prospective, randomized, parallel, three-arm, single-blind trial with two doses of drug compared with control. The protocol was approved by the ethics committees of all the participating institutions, and all patients gave written, informed consent.

End points. The primary safety end points included major adverse cardiac events (MACE) at 30 days and local tissue

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Abbreviations and Acronyms

DES = drug-eluting stent
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MI = myocardial infarction
MS = metallic stent
QCA = quantitative coronary angiography
TSR = target site revascularization
TVF = target vessel failure

effects (incomplete stent apposition, persisting dissection, edge stenosis, and thrombus formation) at 6 months. MACE was defined as a composite of death, myocardial infarction (MI) (more than three times the upper limit of normal creatine kinase levels), and revascularization (surgery or percutaneous coronary intervention) attributed to the target site (the stented and 5-mm persistent segments). When target vessel (the vessel containing the target site) revascularization was included in MACE, the composite end point was renamed "target vessel failure" (TVF).

The primary performance end points were the reduction of in-stent volumetric burden assessed by intravascular ultrasound (IVUS) and reduction of target site diameter stenosis by quantitative coronary angiography (QCA) at six months.

The secondary performance end points were TVF at 6 and 12 months and angiographic binary restenosis at 6 months.

Power calculation and sample size. To detect a difference of 6.6% in diameter stenosis and of 11.5 mm^3 in intimal hyperplasia, with a significance level of 0.05 and 90% power, 110 patients would be needed in each of the three arms. A sample size of 120 patients was chosen.

Patient selection. Patients with stable angina pectoris or silent ischemia and a single de novo lesion in a native coronary artery ≥3.0 mm and ≤4.0 mm in diameter that could be covered by an 18-mm stent were enrolled. Randomization was done by a telephone allocation service.

Study device. The three components of the investigational device were the Multilink Tetra stent, a polymeric coating, and an anti-proliferative drug—actinomycin D (3)—in two doses (2.5 and 10 $\mu g/cm^2$ of metal stent surface area). The eluting profile of actinomycin D is targeted to release 80% of drug in 28 days. Stents were 18 mm in length and 3.0, 3.5, or 4.0 mm in diameter.

Table 1. Baseline Clinical and Angiographic Characteristics

		DES	
	MS (n = 118)	AcD 2.5 $\mu g/cm^2$ (n = 120)	AcD 10 $\mu g/cm^2$ (n = 119)
Age (yrs)	60 ± 10	61 ± 11	60 ± 11
Male gender	78	78	80
Previous MI	41	38	37
Diabetes mellitus*	5	15	11
Treated dyslipidemia	53	58	54
Treated hypertension	50	49	45
Current smoker	30	23	29
Angina pectoris by CCS class†			
I	7	4	4
II	34	34	35
III	21	21	23
IV	15	14	13
Target coronary artery			
LAD	37	44	42
RCA	42	40	35
LCx	21	16	23
Lesion type			
A	7	7	2
B1	23	21	29
B2	66	64	64
C	4	8	5
Reference vessel diameter, baseline (mm)	2.83	2.84	2.91
Lesion length (mm)	11.3	11.6	10.7
MLD, baseline (mm)	1.00	1.01	1.04
Diameter stenosis, baseline (%)	64	64	63

There were no significant differences in the baseline clinical and angiographic characteristics between the three groups, with the exception of diabetes (*difference [95% confidence interval] in incidence of diabetes—control vs. 2.5 $\mu g/cm^2$: −9.9% [−17% to −2.3%]; control vs. 10 $\mu g/cm^2$: −5.8% [−12% to 1.02%]). †Angina was defined according to the system of the Canadian Cardiovascular Society (CCS). In the 2.5- and 10-μg groups, there were seven and eight lesions receiving two actinomycin D stents, respectively. Data are presented as the mean value ± SD or percentage of patients.

AcD = actinomycin D; DES = drug-eluting stent; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; MI = myocardial infarction; MLD = minimal luminal diameter; MS = metallic stent; RCA = right coronary artery.

Table 2. Serial Quantitative Coronary Angiographic Analyses

		DES			
	MS	AcD 2.5 μg/cm²	p Value	AcD 10 μg/cm²	p Value
Angiographic follow-up	65 (55%)	114 (95%)		115 (97%)	
In-stent					
MLD, post-intervention (mm)	2.64 ± 0.34	2.77 ± 0.45	0.02	2.82 ± 0.43	0.002
MLD, f/u (mm)	1.88 ± 0.58	1.76 ± 0.70	0.25	1.90 ± 0.68	0.87
Late loss (mm)	0.76 ± 0.43	1.01 ± 0.58	0.001	0.93 ± 0.58	0.03
Restenosis (%)	11	25	0.03	17	0.38
Edges					
Proximal MLD, post-intervention (mm)	2.60 ± 0.53	2.73 ± 0.58	0.12	2.79 ± 0.56	0.02
Proximal MLD, f/u (mm)	2.32 ± 0.60	2.22 ± 0.67	0.35	2.26 ± 0.76	0.58
Proximal late loss (mm)	0.28 ± 0.38	0.51 ± 0.52	0.002	0.53 ± 0.61	<0.001
Proximal restenosis (%)	3	5	0.71	14	0.02
Distal MLD, post-intervention (mm)	2.31 ± 0.56	2.40 ± 0.58	0.32	2.41 ± 0.58	0.25
Distal MLD, f/u (mm)	2.23 ± 0.53	2.05 ± 0.61	0.05	1.99 ± 0.64	0.009
Distal late loss (mm)	0.08 ± 0.31	0.35 ± 0.50	<0.001	0.43 ± 0.57	<0.001
Distal restenosis (%)	2	4	0.65	6	0.26
Target site*					
DS (%)	35 ± 15	40 ± 18	0.08	40 ± 19	0.05
Restenosis (%)	14	26	0.06	28	0.04
Vessel segment					
RD, f/u (mm)	2.76 ± 0.58	2.71 ± 0.55	0.58	2.78 ± 0.48	0.81
DS, f/u (%)	37 ± 13	41 ± 18	0.11	41 ± 18	0.06
Restenosis rate (%)	14	27	0.04	28	0.04
Median time of angiographic f/u (days)	162 ± 53	161 ± 40	NS	160 ± 41	NS

*Target site diameter stenosis was the primary performance end point in the intention-to-treat analysis.
DS = diameter stenosis; f/u = follow-up; RD = reference diameter; other abbreviations as in Table 1.

QCA and IVUS. The QCA and IVUS analyses were performed as previously described (4,5). Coronary aneurysms were angiographically defined as localized coronary artery dilation ≥1.5 times the reference diameter (4).

Statistical analysis. All analyses were based on the intent-to-treat principle. For continuous variables, the mean value ± SD was presented; differences between the treatment groups were evaluated with the Student *t* test. Discrete variables were expressed as counts and percentages and were analyzed with the Fisher exact test. Event-free survival times were analyzed using the Kaplan-Meier method. Differences between the groups were compared with the use of both the Wilcoxon and log-rank tests.

RESULTS

Patient baseline characteristics. In total, 360 patients were randomly assigned to receive a DES with a dose of 2.5 μg/cm² (n = 120) or 10 μg/cm² (n = 121) or a MS (n = 119). Three patients were de-registered because they did not receive either a DES or control stent. Baseline clinical and angiographic characteristics are presented in Table 1. The significant difference in minimal lumen diameter after the procedure between the MS and DES groups could not be accounted for by procedural differences.

Procedural characteristics and clinical outcomes in the hospital and at one month. The procedural success rate was 99%. In-hospital MACE was confined to the four patients (1.1%) with non–Q-wave MI. The MACE rates at 30 days ranged from 0.8% to 2.5%, without differences between groups.

However, early monitoring of a subset of 39 DES patients revealed an increased rate of target site revascularization (TSR), suggesting that the investigational device was not performing as intended. After the sponsor informed the principal investigator and the Data Safety Monitoring Board, the following recommendations were made: 1) accelerated angiographic follow-up for DES patients; 2) a second angiographic and clinical follow-up visit six months later; 3) possible re-intervention for moderate restenosis (>30% DS); 4) extension of clopidogrel administration for at least a further six months for DES patients; and 5) angiographic and IVUS follow-up was no longer mandatory for MS patients, as primary performance end points could not be reached. Consequently, only 65 of 118 MS patients underwent imaging, and 101 had clinical follow-up at 6 months.

Angiographic outcomes. The in-stent and in-lesion late loss and restenosis rates at six months were higher in both DES groups than in the MS group (Table 2). Aneurysm formation was infrequent, with two cases (3.1%) in the MS group and five (2.2%) in the DES groups.

Clinical outcomes at 12 months. At 12 months, MACE and TVF were higher in the DES than in the MS patients, mainly due to increased TSR (Table 3). Of the 2 deaths, the 1 with a MS was sudden at 44 days, and the 1 with low-dose DES was due to MI at 306 days. After 30 days, there were 2 additional non–Q-wave MIs in the low-dose and 1 in the

Table 3. Most Severe (Hierarchical) and Total Count of Cardiac Events Up to 12 Months in Each Treatment Group

		DES			
	MS (n = 104)*	AcD 2.5 $\mu g/cm^2$ (n = 120)†	p Value	AcD 10 $\mu g/cm^2$ (n = 119)†	p Value
Death	1 (0.8)	1 (0.8)	NS	0	NS
Myocardial infarction					
Q-wave	0	0	NS	0	NS
Non-Q-wave	1 (1.0)	2 (1.7)	NS	4 (3.4)	NS
Target site revascularization					
CABG	1 (1.0)	0	NS	5 (4.2)	NS
PCI	11 (10.6)	37 (30.8)	<0.001	41 (34.5)	<0.001
Hierarchical MACE‡	14 (13.5)	40 (33.3)	<0.01	50 (42.0)	<0.001
Event-free survival	90 (86.5)	80 (66.7)		69 (58.0)	
Target vessel revascularization (CABG and PCI)	3 (2.9)	4 (3.3)	NS	1 (0.8)	NS
Target vessel failure§	17 (16.3)	44 (36.7)	<0.001	51 (42.9)	<0.001
Total count of events	16	45		61	

*Follow-up was no longer mandatory for the MS group; therefore, for 14 patients no follow-up was available. †For five and three patients in the 2.5- and 10-$\mu g/cm^2$ group, respectively, no follow-up case report forms have been received; however, these patients have been contacted and all are alive and had no other MACE in the 12-month follow-up time frame. ‡Includes death, myocardial infarction, target site revascularization. §Includes death, myocardial infarction, target site revascularization, and/or target vessel revascularization. Data are presented as the number (%) of patients.

CABG = coronary artery bypass grafting; MACE = major adverse events; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

high-dose DES arm. To 1 year, there were 14 DES patients who had a second re-intervention, and in 2, a third re-intervention (Fig. 1).

IVUS outcomes. There was late-acquired incomplete stent apposition in six patients in the low-dose group and seven in the high-dose group. At variance with the angiographic findings, there were apparently no differences between groups in volumetric obstruction measured by IVUS. This discrepancy is the result of a biased selection of DES patients undergoing IVUS during follow-up, as demon-

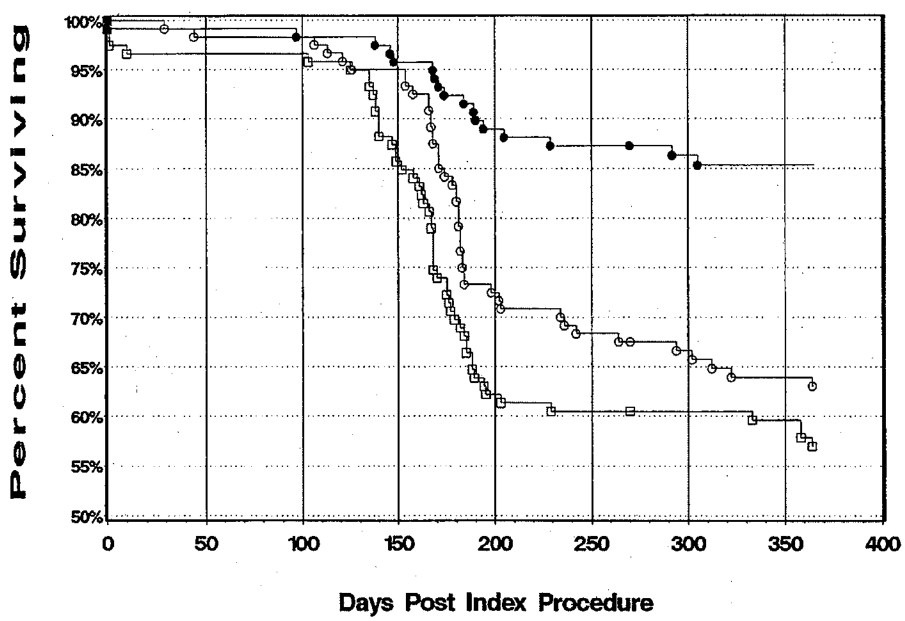

Figure 1. Kaplan-Meier estimates of survival free of repeated target site revascularization up to 365 days among patients who received actinomycin-eluting 2.5 and 10 $\mu g/cm^2$ stents and those who received the metallic stent. The rate of event-free survival was significantly higher in the control stent group than in the actinomycin stent groups ($p < 0.05$ by both the Wilcoxon and log-rank tests). **Solid circles** = control (n = 104); **open circles** = drug-coated, 2.5 $\mu g/cm^2$ drug-eluting stent (n = 120); **squares** = drug-coated, 10 $\mu g/cm^2$ drug-eluting stent (n = 119).

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Table 4. Incidence of Vessel Segment Restenosis in Patients With and Without Intravascular Ultrasound

		DES	
	MS	AcD 2.5 $\mu g/cm^2$	AcD 10 $\mu g/cm^2$
Patients with IVUS	4/39 (10.3)	23/89 (25.8)	22/93 (23.7)
Patients without IVUS	5/26 (19.2)	8/25 (32.0)	11/23 (47.8)
	*p = 0.47	p = 0.61	p = 0.037

*Fischer exact test. Data are presented as n/N (%).
IVUS = intravascular ultrasound; other abbreviations as in Table 1.

strated by the higher binary "vessel segment" restenosis rate (32% and 47.8%) in the DES patients who did not undergo IVUS follow-up, compared with those who did (25.8% and 23.7%) (Table 4). This biased selection invalidated interpretation of the IVUS findings.

DISCUSSION

This trial showed that while in-hospital and one-month outcomes were similar in each group, by six months there was increased restenosis, late lumen loss, and TSR in the DES arm. Despite this increased rate of restenosis, mortality and MI rates were very low.

The safety of the polymer was demonstrated in the porcine coronary model, where the histologic response was similar to MS to 180 days. Drug-eluting stents with four doses of actinomycin D (2.5, 10, 40, and 70 $\mu g/cm^2$) were evaluated in preclinical studies in the porcine coronary model by angiography, histomorphometry, and histopathology at 28 days. At this time, all vessels were patent, and there was marked suppression of neointimal formation above the stent with all doses. Neointimal thickness above the internal elastic lamina was decreased in all dose groups compared with the MS control. Medial thinning and necrosis were observed in the high-dose groups, as was positive remodeling. Intimal fibrin deposition and inflammation were present with all doses, but most marked with the higher doses. Based on these preclinical findings, the two lower doses were considered safe for further evaluation in humans, with three months of data pending, which was the practice for MS extended to DES at the time. This trial has demonstrated that 28-day animal data do not provide sufficient information to judge the safety and efficacy of DES.

Conclusions. This trial demonstrates that not all antiproliferative drugs are effective in the prevention of restenosis. It has become clear that promise in early preclinical studies (30 days) does not necessarily translate into clinical effectiveness at 6 months and that late safety animal data (90 days) is a prerequisite for clinical investigation (6).

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Actinomycin-eluting stent for coronary revascularization: A randomized feasibility and safety study: The ACTION trial

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Carvedilol for Prevention of Restenosis After Directional Coronary Atherectomy : Final Results of the European Carvedilol Atherectomy Restenosis (EUROCARE) Trial

Patrick W. Serruys, David P. Foley, Berthold Höfling, Jacques Puel, Helmut D. Glogar, Ricardo Seabra-Gomes, Javier Goicolea, Pierre Coste, Wolfgang Rutsch, Hugo Katus, Hans Bonnier, William Wijns, Amadeo Betriu, Ulrike Hauf-Zachariou, Eline Montauban van Swijndregt, Rein Melkert and Rudiger Simon

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Carvedilol for Prevention of Restenosis After Directional Coronary Atherectomy

Final Results of the European Carvedilol Atherectomy Restenosis (EUROCARE) Trial

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Background—In addition to its known properties as a competitive, nonselective β and α-1 receptor blocker, carvedilol directly inhibits vascular myocyte migration and proliferation and exerts antioxidant effects that are considerably greater than those of vitamin E or probucol. This provides the basis for an evaluation of carvedilol for the prevention of coronary restenosis.

Methods and Results—In a prospective, double-blind, randomized, placebo-controlled trial, 25 mg of carvedilol was given twice daily, starting 24 hours before scheduled directional coronary atherectomy and continuing for 5 months after a successful procedure. The primary end point was the minimal luminal diameter as determined during follow-up angiography 26±2 weeks after the procedure. Of 406 randomized patients, 377 underwent attempted atherectomy, and in 324 (88.9%), a ≤50% diameter stenosis was achieved without the use of a stent. Evaluable follow-up angiography was available in 292 eligible patients (90%). No differences in minimal luminal diameter (1.99±0.73 mm versus 2.00±0.74 mm), angiographic restenosis rate (23.4% versus 23.9%), target lesion revascularization (16.2 versus 14.5), or event-free survival (79.2% versus 79.7%) between the placebo and carvedilol groups were observed at 7 months.

Conclusions—The maximum recommended daily dose of the antioxidant and β-blocker carvedilol failed to reduce restenosis after successful atherectomy. These findings are in contrast to those of the Multivitamins and Probucol Trial, which raises doubts regarding the validity of the interpretation that restenosis reduction by probucol was via antioxidant effects. The relationship between antioxidant agents and restenosis remains to be elucidated. **(*Circulation.* 2000;101:1512-1518.)**

Key Words: restenosis ■ prevention ■ atherectomy ■ carvedilol ■ angiography ■ β-blocker ■ antioxidants

Pharmacological approaches to a reduction in restenosis after coronary interventions using agents to prevent vascular smooth muscle cell proliferation have been largely ineffective.[1-3] Two trials using antioxidants, one with vitamin E[4] and the other using vitamin E and probucol,[5] reported a reduction in restenosis after balloon angioplasty. This reduction initially had no mechanistic explanation,[5] but a later study suggested an inhibition of vessel remodelling as the possible mode of action.[6]

Carvedilol is a nonselective β-adrenergic receptor antagonist with vasodilating properties that are mediated by α-1 receptor inhibition.[7] It is approved for the treatment of angina pectoris, hypertension, and heart failure. It is also a direct inhibitor of myofibroblast migration in the vascular media and adventitia.[8,9] Significant inhibition of rat carotid intimal hyperplasia after injury, even with acute carvedilol dosing,[10] and of human pulmonary artery vascular smooth muscle cells in culture[8,9] has been reported. Furthermore, carvedilol and its

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A list of all EUROCARE investigators is given in the Appendix.

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metabolites exhibit antioxidant properties that are some 30 to 80 times more potent than vitamin E or probucol.[11-13]

In the EUROCARE trial, this generalized potential for carvedilol to inhibit restenosis was evaluated in patients undergoing successful directional coronary atherectomy (DCA). This procedure was chosen because in 1994, DCA was known to be more effective than balloon angioplasty, but it was limited by a greater tendency toward restenosis.[14-16] Thus, a positive outcome would enhance the clinical usefulness of DCA and could be generalized to other interventions. Equally important, the trial hypothesis could be meaningfully tested using a smaller sample size than would be required in a population undergoing balloon angioplasty.[17]

Methods

Primary and Secondary End Points

The primary end point of EUROCARE was the MLD at angiographic follow-up 26±2 weeks after successful DCA (this was defined by the core laboratory; see below). Secondary end points included MACE[18] at 7 months, angiographic indices of absolute and relative loss in MLD, loss index, restenosis rate, and adverse events.

Study Population

Patients with stable or unstable angina pectoris (except Braunwald Class 3 unstable angina) who were scheduled to undergo elective DCA of a single native primary coronary stenosis were eligible for inclusion. Major exclusion criteria were contraindications to carvedilol (eg, bradycardia <50 bpm, second or third degree atrioventricular block, obstructive airway disease, insulin-dependent diabetes, etc) or to a discontinuation of existing β-blocker therapy, ineligibility for DCA (eg, unprotected left main stem disease and/or vessel size <3 mm), and planned stent implantation. Patients were also excluded if they had a documented myocardial infarction (see Definitions) within the preceding 5 days or intolerance to acetylsalicylic acid (aspirin).

Study Design

The trial was a multicenter, randomized (block size of four), double-blind, parallel-group design. Patients were assigned to fixed oral doses of carvedilol (25 mg BID) or placebo and, before enrolment, were tapered off all previous antihypertensive, vasoactive, and antianginal medication other than nitrates. Treatment started a minimum of 24 hours before the scheduled DCA and was continued for a 5-month period after successful DCA (see Definitions). One month before scheduled follow-up angiography, the study medication was tapered off over a 1-week period (12.5 mg of carvedilol BID or placebo). During the course of the trial, antihypertensive and antianginal therapy could be initiated at the discretion of the investigators. Concomitant therapy with β-blockers, α-blockers, anti-arrhythmics, antioxidants (eg, high-dose vitamin E or C or probucol), antiproliferative agents (eg, cytostatics), drugs that influence the pharmacodynamics or kinetics of carvedilol (ie, psychopharmaceuticals and nonsteroidal anti-inflammatory agents, excluding aspirin and laxatives), or anticoagulants (except heparin during the procedure) was not allowed during the trial.

Compliance was assessed by capsule counts. Trial medication was discontinued in patients who did not have a successful DCA and in those who experienced a MACE (except non-Q wave myocardial infarction) or other serious adverse event. The study was conducted in accordance with the Declaration of Helsinki and the Committee for Proprietary Medicinal Products/Good Clinical Practice Guidelines. The protocol was approved by the ethics committees of all participating centers, and all patients gave written informed consent before inclusion.

DCA Procedure

After sheath introduction, 10 000 IU/L heparin was given; further bolus doses were given as needed to keep an activated coagulation time >350 s. Intravenous doses of 250 mg of acetylsalicylic acid were also administered in patients not already taking 75 to 500 mg daily. DCA was recommended to be guided by on-line quantitative coronary angiography and, where possible, IVUS, with adjunctive balloon angioplasty to achieve optimal results (see Definitions).

Angiographic Procedures and Quantitative Coronary Angiography at the Core Laboratory

Angiographic procedures and core laboratory evaluations were strictly standardized, as has been described in previous trials.[2,3,14,16] After intracoronary nitrate bolus injection, the target stenosis was filmed in a minimum of 2 projections before and after the procedure; these projections were repeated identically at follow-up. The Cardiovascular Angiographic Analysis System II (Pie Medical) was used for the angiographic analysis at the core laboratory, using a well-described methodology.[2,3,14,16]

Clinical Assessments

Patients returned for clinical follow-up visits at 1, 5, 6, and 7 months. Shortly before reangiography, a symptom-limited exercise tolerance test was performed. To monitor the safety of trial medication, serial recordings of creatinine, alkaline phosphatase, γ-galactosyl transferase, glutamic pyruvic transaminase, and glutamic-oxaloacetic transaminase were assessed at each visit. Cardiac enzymes were determined when clinically indicated and according to local practice. Adverse events were recorded continuously, whether or not they were considered drug-related.

Definitions

Successful DCA was defined off-line by the core laboratory as ≤50% diameter stenosis; optimal DCA indicated ≤20% diameter stenosis in every angiographic view, without the use of a stent or the occurrence of a MACE, which was defined as cardiac death, myocardial infarction, coronary artery bypass graft surgery, or reintervention at the site of the original DCA (target lesion revascularization).[18] Myocardial infarction was defined as development of new pathological Q waves and/or an increase of more than twice the upper limit of normal of levels of creatine kinase, with concomitant elevation of the MB fraction. Compliance with trial medication was defined as consumption of >80% of trial medication in the first month and >75% of medication thereafter.

Statistical Methods

Sample size calculation was based on a postulated difference in MLD at follow-up between the placebo and carvedilol groups of 0.20±0.62 mm (mean MLD: control group, 1.76 mm[14] and carvedilol group, 1.96 mm), which is equivalent to a 30% reduction in restenosis rate. A sample size of 152 patients per group would be required to detect such a difference with a power of 0.80 and a 2-sided α of 0.05. To allow for nonevaluable patients, we decided to recruit 400 total patients.

As specified in the protocol, the analysis was based on the intention-to-treat principle; this then included all patients who took ≥1 tablet of study medication, underwent successful DCA, and had an analyzable follow-up angiogram. Safety evaluation included all randomized patients who took ≥1 dose of study medication. Student's t test was used for intergroup comparisons of continuous measurements, and the χ^2 test was used for categorical variables. Frequency distribution curves are used to display MLD measurements before and after DCA and at follow-up, and Kaplan-Meier survival curves illustrate freedom from MACE.

Results

Procedural Results

From December 1994 to February 1997, 406 patients were randomized to receive ≥1 dose of trial medication (206 took

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Randomized

406 → **Withdrawn consent before intervention** N = 4

	Carvedilol	Placebo
Withdrawn consent	2	2

402 → **MACE before interventional attempt** N = 1

	Carvedilol	Placebo
MI + dead	1	0

401 → **No interventional attempt** N = 10

	Carvedilol	Placebo
Lesion not suitable for percutaneous intervention	0	6
No lesion	1	3

391 → **No DCA, but other technique** N = 14

	Carvedilol	Placebo
PTCA	3	4
Stent	3	3
Unknown	0	1

377 → **Failed DCA attempt** N = 16

	Carvedilol	Placebo
Technical problem with puncture	0	1
No guiding support	6	3
Could not cross lesion with wire	0	1
Could not cross lesion with device	1	4

361 → **Complication after DCA during intervention** N = 35

	Carvedilol	Placebo
Emergency CABG → death	1	0
Perforation → death	0	1
Emergency CABG	1	3
Bail-out stent	16	13

326 → **Suboptimal result after DCA** N = 2

	Carvedilol	Placebo
DS (DS>50% + stent)	2	0

324

Figure 1. Flow chart showing derivation of the intention-to-treat population. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and DS, diameter stenosis.

carvedilol and 200 took placebo). Among these, 377 underwent attempted DCA (Figure 1). One patient died after coronary perforation, and 5 were referred for emergency coronary artery bypass grafting. One of these 5 patients died perioperatively. Successful bailout stenting was performed in 29 patients.

Of the 324 patients with successful DCA (Table 1), 292 (90%) had an evaluable follow-up angiogram; these 292 patients made up the trial population. Quantitative angiographic baseline and procedural parameters are shown in Tables 2 and 3. Predilatation was performed in 6% of patients. A 7-French device was used in 84% of cases. A median of 13 cuts were done (interquartile range, 9 to 30), and a maximum of 4.8 atm of balloon pressure (range, 1 to 8 atm) was applied. Postdilatation was performed in 66% of cases using a mean balloon size of 3.65±0.50 mm at a maximal pressure of 8.2±3.19 mm and a balloon-to-artery ratio of 1.08±0.15 mm. An optimal result was reported by the investigator in 68% of cases and by the core laboratory (determined by ≤20% diameter stenosis) in 26% of cases.

In the intention-to-treat population, 132 patients in the carvedilol group (78%) and 127 in the placebo group (81.9%) were compliant.

TABLE 1. Demographics and Baseline Characteristics

	Carvedilol (n=169)	Placebo (n=155)	All
Male sex	147 (87)	137 (88.4)	284 (87.7)
Age, y	57.9±10.0	58.6±9.7	58.2±9.8
Smoking			
Never smoked	42 (24.9)	51 (32.9)	93 (28.7)
Previous smoker	95 (56.2)	72 (46.5)	167 (51.5)
Current smoker	32 (18.9)	32 (20.6)	64 (19.8)
Diabetes mellitus	17 (10.1)	14 (9)	31 (9.6)
Hypercholesterolemia	36 (21.3)	22 (14.2)	58 (17.9)
Other hyperlipidemia	32 (18.9)	30 (19.4)	62 (19.1)
Hypertension	50 (29.6)	43 (27.7)	93 (28.7)
Previous MI	84 (49.7)	56 (36.1)	140 (43.2)
Previous PTCA	0 (0.0)	1 (0.6)	1 (0.3)
Previous CABG	0 (0.0)	4 (2.6)	4 (1.2)
Peripheral vascular disease	5 (3.0)	9 (5.8)	14 (4.3)
Medication			
Calcium antagonists	40 (23.7)	50 (32.3)	90 (27.8)
ACE inhibitors	38 (22.5)	34 (21.9)	72 (22.2)
β-Blockers	105 (62.1)	97 (62.6)	202 (62.3)
Nitrates	128 (75.7)	107 (69)	235 (72.5)

Values are n (%) or mean±SD. MI indicates myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; and ACE, angiotensin-converting enzyme.

Late Outcomes

No differences in the minimal luminal diameter (MLD), angiographic restenosis rate (Table 3 and Figure 2), or the occurrence of major adverse cardiac events (MACE) between the placebo and carvedilol groups were observed during a follow-up of ≤7 months (Table 4 and Figure 3).

Other Adverse Events

No difference in the incidence of adverse events was observed between the groups (carvedilol, 50%; placebo, 47.5%), although a higher incidence of hypotension (7.3% versus 1%) and bradycardia (6.3% versus 0%) existed in the carvedilol group.

TABLE 2. Baseline Angiographic Characteristics

	Carvedilol (n=169)	Placebo (n=155)
AHA/ACC lesion type		
A	12 (7.1)	11 (7.1)
B1	63 (37.5)	65 (41.9)
B2	93 (55.4)	79 (51.0)
C	0 (0.0)	0 (0.0)
No. of diseased vessels		
1	140 (83.8)	126 (81.2)
2	21 (12.6)	16 (10.4)
3	6 (3.6)	13 (8.4)
Calcification	47 (27.8)	31 (20.0)
Thrombus	5 (3.0)	3 (2.0)
Lesion length, mm	8.39±2.57	8.71±3.04
Vessel size, mm	3.36±0.56	3.49±0.61

Values are n (%) or mean±SD. AHA indicates American Heart Association, and ACC, American College of Cardiology.

TABLE 3. Acute and Follow-Up Angiographic Indices

	Carvedilol (n=154)	Placebo (n=138)
Reference diameter, mm		
Preoperative	3.38±0.57	3.48±0.59
Postoperative	3.56±0.51	3.61±0.56
Follow-up	3.25±0.59	3.20±0.61
MLD, mm		
Preoperative	1.19±0.34	1.26±0.44
Postoperative	2.77±0.49	2.85±0.50
Follow-up*	1.99±0.73	2.00±0.74
Diameter stenosis, %		
Preoperative	64.33±9.78	63.56±11.27
Postoperative	22.19±7.71	20.86±7.94
Follow-up†	39.13±17.93	37.54±18.35
Acute gain, mm	1.58±0.51	1.59±0.50
Late loss, mm	0.77±0.70	0.85±0.70
Relative loss, mm	0.23±0.21	0.25±0.21
Loss index	0.51±0.49	0.55±0.48
Restenosis rate, %	23.4	23.9

Values are mean±SD, unless otherwise indicated.
*P=0.92; †P=0.46.

Discussion

Despite the extensive in vitro and in vivo evidence for a potential benefit of carvedilol (through the inhibition of myofibroblast migration in the media and adventitia and of free radical–mediated vascular inflammation and remodelling, as well as its direct antiproliferative effects[7–13]), the maximum recommended daily dosage failed to reduce restenosis after successful DCA. Because carvedilol and its metabolites have considerably greater antioxidant effects than vitamin E or probucol,[11–13] each of which have been reported to reduce restenosis after balloon angioplasty,[4,5] the purported antioxidant mechanism of probucol for the observed selective

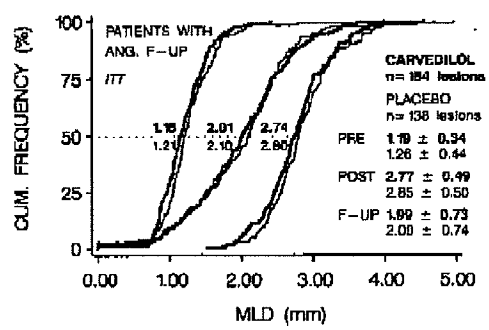

Figure 2. Cumulative frequency curves of MLD before (PRE) and after (POST) successful DCA and at follow-up (F-UP). Mean values (±SD) are on the right, and median values are next to the curves. CUM indicates cumulative; ITT, intention-to-treat; and ANG, angiographic.

TABLE 4. MACE in Each Group at 7-Month Follow-Up

	Carvedilol (n=169)	Placebo (n=155)
Death	0 (0.0)	2 (1.3)
MI	5 (3.0)	5 (3.2)
Q wave MI	1 (0.6)	0 (0.0)
Non-Q Wave MI	4 (2.4)	5 (3.2)
CABG	3 (1.8)	3 (1.9)
Re-PTCA (TLR)	26 (15.4)	24 (15.5)
No MACE	135 (79.9)*	121 (78.1)*

Values are n (%). MI indicates myocardial infarction; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; and TLR, target lesion revascularization.

*P=0.64 by Wilcoxon rank sums test at 240 days.

benefit in the Multivitamins and Probucol Trial in Prevention of Restenosis Post Percutaneous Coronary Angiography seems putative.[6] On the basis of the neutral outcome of this trial, we think that in the probucol trial, either another mechanism was responsible for the observed reduction in renarrowing or the outcome was serendipitous. In addition, it must be concluded that the role of systemic antioxidants for the prevention of restenosis is debatable and must be further elucidated.

The question arises as to why no effect was observed in this multicenter clinical trial of an agent that has greater antioxidant effects than probucol[11-13] in addition to its other listed effects.[7-10] First, although it may be claimed that the rat model is not an ideal in vivo platform for a clinical trial, this trial hypothesis was based on the combined evidence from many other studies,[7-13] as well as the acceptability of this drug for clinical use.

Adequacy of Dose and Pretreatment Period

Carvedilol reaches peak plasma levels 2 hours after an oral dose of 25 mg, and steady-state plasma levels are achieved after 5 half-lives of ≈7 hours each,[7] which is a 35-hour period. In this trial, for practical purposes, patients were pretreated for a minimum of 24 hours, undergoing DCA within 2 hours after taking the third dose of trial medication. Thus, although a steady-state plasma level of carvedilol may

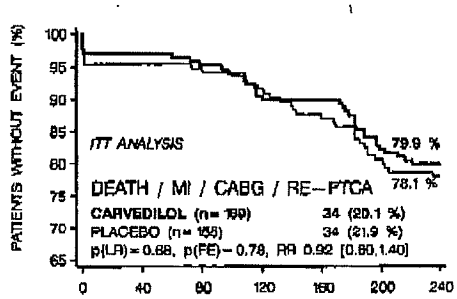

Figure 3. Kaplan-Meier estimates of freedom from death, myocardial infarction (MI), coronary artery bypass grafting (CABG), and repeat angioplasty (Re-PTCA). LR indicates log ranking; F(E), Fischer exercise test; and RR, relative risk.

not yet have been reached in all patients, DCA was usually performed to coincide with peak plasma levels, and carvedilol accumulates rapidly in the lipid environment, including cell membranes and the lipid moiety of lipoproteins.[7,19] In a trial that used a dose regimen similar to that of this trial, 84% suppression of neointimal hyperplasia was observed in the rat carotid artery balloon angioplasty model, with pretreatment for only 2 hours before and 14 days after balloon angioplasty.[10] Additionally, protection by carvedilol from oxygen free-radical–induced damage has been demonstrated at concentrations that are consistent with the plasma levels of the drug attained in patients on a dose of 25 to 50 mg a day (ie, 100 to 300 nmol/L).[13] Furthermore, clinical studies have recently demonstrated that carvedilol creates a marked reduction in low-density lipoprotein oxidation in hypertensive patients[19] and helps stop the development of nitrate tolerance, which is associated with superoxide anion production.[20] Thus, it can be assumed that the pretreatment and dose regimen should have been sufficient to reproduce, in humans, the experimental effects observed in vitro and in animals.

It is also important to note that the trial medication was safe; no differences between groups existed in the incidence of adverse events, except hypotension and bradycardia. This led to discontinuation of carvedilol in only 3.9% of patients, which is not untoward given that carvedilol is a vasodilating β-blocker.

Appropriateness of DCA-Treated Patients for This Trial

At the time this trial was planned, it was known that DCA achieved greater acute results but was limited by a greater tendency toward renarrowing when compared with conventional balloon angioplasty.[14-16] Stenting was in the early phase of clinical evaluation: the Belgian Netherlands Stent Study (BENESTENT) and Stent Restenosis Study (STRESS) had not yet been completed; thus, stenting was only performed as a bailout procedure, which indicated a failed DCA. The mean luminal loss observed after DCA by the core laboratory was 0.81 mm,[14,16] which is >2 times the average after balloon angioplasty.[2,3,14,16] Before intravascular ultrasound (IVUS) studies, which changed our perception of restenosis,[21-23] we assumed this renarrowing was due to neointimal hyperplasia.[24] For this reason, the investigation of an agent with antioxidant, antichemotactic, and direct antiproliferative effects seemed ideally suited to an atherectomy-treated patient population. IVUS studies have since demonstrated that vessel remodelling may account for >50% of the luminal renarrowing response after DCA,[21,22] which reduces the target for antiproliferative drugs. However, if the report by Côté et al[6] on probucol is correct, the antioxidant effects of carvedilol should have the potential to inhibit vascular remodelling as well as inflammation such that a general reduction of the response to injury could have been reasonably expected.[7-13,19,20]

Because the pretreatment and dose regimen used seems adequate, it can only be speculated that the many alternative pathway cascades that lead to vascular remodelling and neointimal hyperplasia have the capacity to overcome spe-

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cific inhibitory agents to achieve what is essentially an effective natural wound healing response.[23]

Comparison of Atherectomy Results With Other Trials

Although the present study is not a trial asserting the specific value of atherectomy (because DCA is now used in <2% of patients undergoing percutaneous therapics), it is appropriate to compare the short- and long-term results with those of other trials. Procedural success was obtained in 88.9% of cases, as compared with 92% in the Balloon versus Optimal Atherectomy Trial (BOAT).[25] The MLD after the procedure was 2.81 mm in this trial and 2.82 mm in BOAT; in the subgroup of patients with "optimal atherectomy," the MLD after the procedure was 3.09 mm in this trial compared with 3.16 mm in the Optimal Atherectomy Restenosis Study (OARS).[26] The late loss (0.81 mm) in EUROCARE was substantially less than that in both BOAT (0.96 mm) and OARS (1.18 mm), so the restenosis rate in EUROCARE is also lower (23.6%) than that in BOAT (31.4%) and OARS (28.9%). The incidence of target lesion revascularization in EUROCARE (17.1%) was slightly lower than that in BOAT (21.1%) and similar to that in OARS (17.8%). Thus, the level of intervention by DCA that was performed in this trial was representative of the concurrent best clinical practice, and an adequate platform was created for testing an anti-restenosis strategy.

Limitations

Because this was an atherectomy study, it would have been ideal to have IVUS guidance; however, in 1994, IVUS was not yet widely used and, given the lack of difference in outcome between the groups, it would not have changed the outcome of the trial. Also, the antioxidant activity of carvedilol was not measured in this trial because the previously accumulated specific studies of antioxidant effects[7-10,20,21] were considered sufficient evidence to assume a greater clinical effect in this regard than vitamin E or probucol.

Conclusions

Carvedilol was safe and well tolerated by patients undergoing DCA, both during the procedure and in the follow-up period. Despite extensive evidence depicting its potent antioxidant, antichemotactic, and antiproliferative effects, the maximum recommended daily dosage failed to demonstrate any reduction in restenosis as measured by quantitative angiographic and clinical parameters. These results question the validity of the explanation that the reported reduction in restenosis by probucol in the Multivitamins and Probucol Trial was via antioxidant mechanisms. The relationship between antioxidant agents and restenosis remains to be elucidated.

Appendix

Participating Investigators, Listed in Order of Recruitment

Prof Höfling and Dr Engelmann, Klinikum Grosshadern, München, Germany; Prof Puel and Dr Marco, Hôpital Purpan, Toulouse, France; Prof Glogar and Dr Hassan, Allgemeines Krankenhaus der Stadt, Vienna, Austria; Prof Kiel and Dr Alexander, Christian Albrechts Universitätsklinik, Kiel, Germany; Prof Serruys, Dr de Feyter, and Dr Foley, Thoraxcentre Academic Hospital Dijkzigt, Rotterdam, The Netherlands; Prof Seabra-Gomes, Hospital de la Santa Cruz, Linda-a-Velha, Portugal; Dr Macaya and Dr Goicolea, Hospital Clinico San Carlos, Madrid, Spain; Dr Coste, CHRU Bordeaux, Talence, France; Prof Rutsch, Paraskevaides, University Hospital Charité, Berlin, Germany; Prof Katus and Dr. Brachmann, University Hospital, Heidelberg, Germany; Dr Bonnier, Catharina Ziekenhuis, Eindhoven, The Netherlands; Dr Wijns and Dr Heyndrickx, Onze Lieve Vrouw Ziekenhuis, Aalst, Belgium; Dr Betriu, Hospital Clinico I Provincial, Barcelona, Spain; Dr Anivarro, Hospital Universario Vall d'Hebron, Barcelona, Spain; Dr Hertzfeld, Karolinska Hospital, Stockholm, Sweden; Prof Schroeder and Dr Chenu, Hôpital Universitaire de Mont-Godinne, Yvoir, Belgium; Dr Haude, Universität Essen, Germany; Prof de Scheerder, UZ St Raphael-Gasthuisberg, Leuven, Belgium; Dr Waas, University Hospital Giessen, Belgium; Prof Providencia, Hospitals da Universidade de Coimbra, Portugal; and Dr Horstkotte, Universitätsklinikum Benjamin Franklin, Berlin, Germany.

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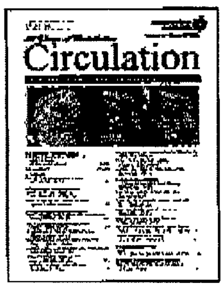

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